cellulose, hydroxypropyl cellulose, hydroxypropyl-ethyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxymethyl cellulose, cellulose acetate, sodium alginate, polymaleic anhydride esters, polyortho esters, polyethyleneimine, polyethylene glycol, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide,poly(1,3 bis(p-carboxyphenoxy) propane-co-sebacic anhydride, N,N-diethylaminoacetate, block copolymers of polyoxyethylene and polyoxypropylene. The microspheres are coated with a (d,1 lactide-glycolide) copolymer. The coating makes the microspheres more resistant to enzymatic degradation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . to entrap other growth hormones in a polymer matrix, e.g. estrogens, androgens, insulin, IGF, interleukin-I and interleukin-II. Cytokins such as **interferon-**.**beta**.and **interferon**-.gamma., used in the **treatment** of diseases such as **osteoporosis**, diabetes mellitus and multiple sclerosis may also benefit from the present invention.

=> d his

(FILE 'HOME' ENTERED AT 16:02:18 ON 20 MAY 1998)

FILE 'USPATFULL, EMBASE, MEDLINE, CAPLUS, WPIDS' ENTERED AT 16:05:21 ON 20 MAY 1998

```
L1       279237 S BONE DISORDER OR (PAGET? DISEASE) OR RICKET? OR OSTEO?
L2       156370 S INTERFERON? OR INTERFERON INDUCER
L3         1977 S L1 AND L2
L4          536 S L1 (10A) L2
L5          108 S L4 (10A) TREAT?
L6            2 S L5 (10A) INTERFERON BETA
L7            2 DUP REM L6 (0 DUPLICATES REMOVED)
L8        97646 S (MAMMARY ORLUNG OR PROSTATE OR THYROID OR RENAL OR COLO
L9            0 S L8 (10A) L5
L10           0 S L8 AND L5
L11         130 S L8 AND L3
L12         124 DUP REM L11 (6 DUPLICATES REMOVED)
L13          43 S L12 AND (INTERFERON BETA OR IFN?)
L14          19 S L12 AND INTERFERON BETA
```

=> d l14 1-19 bib abs kwic

L14 ANSWER 1 OF 19 USPATFULL

AN 1998:51204 USPATFULL

TI Immunotherapeutic stress protein-peptide complexes against cancer

IN Srivastava, Pramod K., Riverdale, NY, United States

PA Mount Sinai School of Medicine Of The City University of New York, New York, NY, United States (U.S. corporation)

PI US 5750119 980512

AI US 94-315892 940930 (8)

RLI Continuation-in-part of Ser. No. US 94-180685, filed on 13 Jan 1994

DT Utility

EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Bansal, Geetha P.

LREP Pennie & Edmonds LLP

CLMN Number of Claims: 48

ECL Exemplary Claim: 1,2

DRWN No Drawings

LN.CNT 1097

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method for inhibiting the proliferation of a tumor in a mammal. The method involves the steps of (a) isolating a stress protein-peptide complex from tumor cells previously removed from the mammal and (b) administering the isolated stress protein-peptide complex back to the mammal in order to stimulate in the mammal an immune response against the tumor from which the complex was isolated. Stress protein-peptide complexes having particular utility in the practice of the instant invention include the Hsp70-peptide, Hsp90-peptide and gp96-peptide complexes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-10 (IL-10), interleukin-11 (IL-11), interleukin-12 (IL-12), **interferon** .alpha. (IFN.alpha.), **interferon** .**beta**. (IFN.beta.), **interferon** .gamma. (IFN.gamma.), tumor necrosis factor .alpha. (TNF.varies.), tumor necrosis factor .beta. (TNF.beta.), granulocyte colony stimulating factor (G-CSF), granulocyte/macrophage colony stimulating. . .

SUMM . . . treatment of a variety of tumors, for example, tumors that are mesenchymal in origin (sarcomas) i.e., fibrosarcomas; myxosarcomas; liposarcomas; chondrosarcomas; **osteogenic** sarcomas; angiosarcomas; endotheliosarcomas; lymphangiosarcomas; synoviosarcomas; mesotheliosarcomas; Ewing's tumors; myelogenous leukemias; monocytic leukemias; malignant lymphomas; lymphocytic leukemias; plasmacytomas; leiomyosarcomas and rhabdomyosarcoma.

SUMM . . . interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-10 (IL-10), interleukin-11 (IL-11), interleukin-12 (IL-12), **interferon** .alpha. (IFN.alpha.), **interferon** .alpha. (IFN.beta.), **interferon** .gamma. (IFN.gamma.), tumor necrosis factor a (TNF.varies.), tumor necrosis factor .beta. (TNF.beta.), granulocyte colony stimulating factor (G-CSF), granulocyte/macrophage colony stimulating. . .

CLM What is claimed is:

22. The method of claim 1, 3, 4, 5, 7, or 8 wherein the **tumor** is a **renal** cell carcinoma.

28. The method of claim 9 or 10 wherein the **tumor** is a **renal** cell carcinoma.

L14 ANSWER 2 OF 19 USPATFULL

AN 1998:36350 USPATFULL

TI Flow cytometric pharmacosensitivity assay and method of cancer treatment

IN Medenica, Rajko D., One Ocean Point, Port Royal Plantation, Hilton Head Island, SC, United States 29928
Powell, David K., 95 Headlands Dr., Hilton Head Island, SC, United States 29926

PI US 5736129 980407

AI US 95-559812 951117 (8)

DT Utility

EXNAM Primary Examiner: Walsh, Stephen; Assistant Examiner: Pak, Michael D.

LREP DeWitt Ross & Stevens SC

CLMN Number of Claims: 14

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2750

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of treating cancer by the use of a multidrug

chemotherapeutic regimen determined by in vitro pharmacosensitivity tests. A cell suspension is prepared from a tumor specimen obtained from the patient. The viable tumor cell count within the cell suspension is calculated. The volume of the cell suspension is then adjusted to obtain a base cell concentration by diluting the cell suspension with patient medium in proportion with the viable tumor cell count. A sample of the cell suspension is retained as a negative control sample. Drug samples are then prepared, each drug sample containing a mixture of cell suspension, patient medium, and a drug selected from several drugs, wherein each drug sample contains a different drug which is added to the drug sample in an aliquot amount proportional to the base cell concentration. The drug samples and negative control sample are then incubated. After incubation, the drug samples and negative control sample are stained with a DNA intercalating dye. The cell viability in the drug samples and negative control sample is determined by use of a flow cytometer. The cell viability in the drug samples and negative control sample is compared to determine the pharmacosensitivity of the tumor. A multidrug treatment regimen is then administered to the patient, wherein the regimen includes the drugs shown to be most effective against the tumor in the pharmacosensitivity assay. The treatment has been shown to be especially useful in the simultaneous treatment of primary tumors and their metastases, especially when the chemotherapeutic regimen is administered locoregionally by intra-arterial infusion methods.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Other researchers have similarly investigated the effects of certain biological response modifiers, e.g., **interferons**, on apoptosis. Dao et al. (1994); Thoth et al. (1992); Fluckiger et al. (1994).

SUMM . . . and lower levels of tumor growth factors such as insulin-like growth factor I. Perhaps the best-known biological response modifiers are **interferons**, a family of over 50 closely related glycoproteins with antiviral, immunoregulatory and antiproliferative functions. The immunoregulatory functions of **interferons**, such as the enhancement of natural killer lymphocyte activity, the increase in histocompatibility antigens, the activation of monocytes/macrophages, and B. . . . proven to be of clinical importance, for example, in protecting bone marrow from the toxicity of chemotherapy. As an example, **interferon** alpha (IFN.alpha.) has been found to result in a considerable percentage of clinical remission alone or in combination with other. . .

SUMM nHuIFN.alpha. (natural human leukocyte **interferon** alpha), by Virogen A. G. (Basel, Switzerland);

SUMM nHuIFN.alpha.n-3 (natural human leukocyte **interferon** alpha n-3), by Purdue Frederick Co. under the trademark "ALFERON" (Norwalk, Conn. 06856);

SUMM nHuIFN.beta. (natural human **interferon beta** or natural human fibroblastic **interferon**), by Virogen Labs., Basel, Switzerland;

SUMM rIFN.alpha.-2a (recombinant **interferon** alpha-2a), by Roche Laboratories, a division of Hoffman-LaRoche Inc. (Nutley, N.J. 07110) under the trademark "ROFERON-A";

SUMM rIFN.alpha.-2b (recombinant **interferon** alpha-2b), by Schering Corp. (Kenilworth, N.J. 07033) under the trademark "INTRON-B";

SUMM rIFN.beta.-1b (recombinant **interferon beta**-1b or fiblaferon), by Berlex Labs. (Richmond, Calif. 94804) under the trademark "BETASERON";

SUMM rIFN.tau.-1b (recombinant **interferon** gamma-1b or polyferon), by Genentech, Inc. (San Francisco, Calif. 94080) under the trademark "ACTIMMUNE";

SUMM nHuIFN.pi.-(natural human **interferon** pi, or antitumor specific **interferon**), the subject of copending U.S. patent application 07/179,529;

SUMM . . . the breast, head, neck, lung, cervix, penis, prostate, testis, and bladder; acute lymphocytic leukemia; meningeal leukemia; non-Hodgkin's lymphoma; mycosis fungoides; **osteosarcoma**; and trophoblastic tumors.

SUMM . . . doxorubicin is an antitumor antibiotic commonly used for treating bladder, breast, head, neck, liver, lung, ovarian, prostatic, stomach, testicular and **thyroid cancer**, as well as Hodgkin's disease, leukemia, Wilm's tumor, lymphomas and sarcomas.

SUMM . . . of the colon, rectum, breast, ovarian, cervix, bladder, stomach, liver and pancreas, 5-FU has synergistic interaction with other antineoplastic agents, **interferons**, and irradiation and is thus commonly used in combination therapy.

SUMM . . . N.J. 08560): an immunomodulator/immunopotentiator; commonly used in combination with 5-FU after surgical resection in Dukes' stage C (tumor-node-metastasis stage III) **colon cancer**.

SUMM . . . or liquid form. Examples of the tumors which have been treated or tested by use of the invention are: bladder **cancer**; breast **cancer**; **colon** carcinoma; non-small cell lung cancer; pancreatic cancer; liver cancer (metastases); prostatic carcinoma; acute myeloid leukemia; chronic myelogenous leukemia; chronic lymphocytic leukemia; hepatocellular carcinoma; glioblastoma; non-Hodgkin's lymphoma; melanoma; **osteogenic** sarcoma; ovarian carcinoma; pleomorphic adenocarcinoma; and Waldenstrom's macroglobulinemia. All have responded to treatment with the procedure. It is expected that. . .

SUMM . . . response modifier drugs plus one or two biological response modifiers. Treatments wherein four non-biological response modifier drugs plus an alpha **interferon** (and occasionally an additional biological response modifier, generally a hormone) have been tested with excellent results, some of which are. . .

DETD Experiment 24: Patient (24) suffered from **osteogenic** sarcoma. A tumor sample was tested by the preferred embodiment of the pharmacosensitivity assay as set out above and the. . .

DETD . . . the assay, 5 of these being biological response modifiers. All 78 patients' tumors demonstrated sensitivity to doxorubicin, mito-C, cisplatin and **interferon** alpha (IFN.alpha.). Patients with the following tumors also demonstrated sensitivity to the following drugs: carboplatin for ovarian and lung **cancer**; floxuridine for **colon cancer**; methotrexate for breast and salivary gland cancer; dacarbazine for melanoma; etoposide for renal cell and primary liver cancer; and bleomycin. . .

DETD . . . Drug sensitivity to the same drugs varied considerably amongst the patients. The four most active drugs for each patient, plus **interferon** alpha (IFN.alpha.) were administered to each patient, and each drug was administered at the highest recommended dosage. Systemic chemotherapy was. . .

DETD . . . with 30 drugs (including 6 biological response modifiers and 3 hormones). Doxorubicin, methotrexate, floxuridine, streptozotocin, BCNU, mito-C, cis-platinum, carboplatin, and **interferons** alpha and gamma (IFN.alpha. and IFN.tau.) were found to have activity in the pharmacosensitivity assay. A percutaneously introduced intra-arterial, intra-hepatic. . .

DETD Experiment 32: 21 patients suffering from **colon cancer** with liver metastases were treated by the procedure (average age 61, from 35-75 years of age, 8 females, 13 males).. . . tumor cells with 26 drugs (5 of which were biological response modifiers). Doxorubicin, methotrexate, fluoruracil,

floxuridine, BCNU, ara-C, streptozotocin and **interferon** alpha (IFN.alpha.) were found to have good activity against the **colon cancer** cells. The 5 most active drugs for each patient and **interferon** alpha were administered once every 4 weeks for 6 weeks by intra-arterial, intra-hepatic catheter, and also by general systemic administration.

DETD . . . and thrombocytopenia) were observed and were reversible. The experiment showed that the procedure offers an effective choice of drugs for **colon cancer** with liver metastases with minimal side-effects.

DETD . . . artery immediately after placement of the catheter and before chemotherapy. Liver tumor cells demonstrated sensitivity to doxorubicin, mito-C, cisplatin and **interferon** alpha in the pharmacosensitivity assay and were used for all 86 patients. Two additional drugs (as per patient tumor response). . .

DETD Dao et al., "Natural human **interferon**-augments apoptosis in activated T-cell line," Cellular Immunology, v155: 304-311 (1994).

DETD Thoth et al., "Type I **interferon** resistance in a colorectal cancer cell line is associated with a more aggressive phenotype in vivo," British Journal of Cancer,. . .

CLM What is claimed is:

14. The method of claim 1 wherein in step (i) an alpha **interferon** and a hormone are administered.

L14 ANSWER 3 OF 19 USPATFULL

AN 1998:7097 USPATFULL

TI Antitumor agent

IN Arai, Shigeyuki, Okayama, Japan
Nishizaki, Yasushi, Okayama, Japan
Kimoto, Tetsuo, Okayama, Japan
Kurimoto, Masashi, Okayama, Japan

PA Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Okayama, Japan (non-U.S. corporation)

PI US 5710179 980120

AI US 96-675059 960703 (8)

PRAI JP 95-191015 950405

DT Utility

EXNAM Primary Examiner: Goldberg, Jerome D.

LREP Browdy and Neimark

CLMN Number of Claims: 3

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 469

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An antitumor agent comprising as an effective ingredient 3-[4-hydroxy-3,5-bis(3-methyl-2-butenyl)phenyl]-2-propenoic acid obtained from propolis and/or its physiologically acceptable salt(s). The agent exerts a strong antitumor activity without substantially inducing side effects.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . its salt(s), as well as compositions with one or more carries, excipients, diluents, stabilizers, and biologically active substances such as **interferon**-.alpha., **interferon**-.**beta**., **interferon**-.gamma., interleukin-2, interleukin-12, TNF-.alpha., TNF-.beta., cyclophosphamide, adriamycin, .alpha.-difluoromethylornithine, melphalan, 5-fluorouracil, doxorubicin, chlorambucil, vinblastine, 1,3-bis(2-chloroethyl)-1-nitrosourea, cisplatin, levamisole, D-penicillamine, gold compounds, BCG, KRESTIN.RTM.. . .

SUMM The present antitumor agent exerts a strong antitumor activity on human malignant tumors, for example, solid **tumors** such as **colon cancer**, rectum **cancer**,

Gastric **cancer**, **thyroid** gland **cancer**
, lingual cancer, bladder cancer, choriocarcinoma, cancer of liver, uterine cancer, prostatic cancer, pharyngeal cancer, lung cancer, breast cancer, malignant melanoma, Kaposi sarcoma, brain tumor, neuroblastoma, ovarian tumor, testicular tumor,
osteosarcoma, pancreatic **cancer**, **renal**
carcinoma, hypernephroma, and angioendothelioma; and hematopoietic malignant tumors such as leukemia and lymphoma.

SUMM . . . 0.85)
100 (42.8)
(ATCC HB 8065)
HeLa cell (uterine cancer)
0.54 .+-. 0.06 (1.36 .+-. 0.61)
100 (100)
(ATCC CCL 2)
RPMI 4788 cell (**colon cancer**)
0.21 .+-. 0.03 (2.95 .+-. 1.36)
100 (71.4)
(FERM BP-2429)
WiDr cell (rectum cancer)
0.36 .+-. 0.02 (1.83 .+-. 0.85)
100 (85.7)
(ATCC CCL 218)
KB cell (rhinopharynx cancer)
0.54 .+-. 0.03 (2.12 .+-. 0.96)
100 (42.8)
(ATCC CCL 17)
Hep-2 cell (**thyroid** gland **cancer**)
0.81 .+-. 0.65 (2.16 .+-. 1.31)
100 (42.8)
(ATCC CCL 23)
G-361 cell (malignant melanoma)
0.36 .+-. 0.02 (1.96 .+-. 0.98)
100. . .

SUMM . . . only a relatively low dose on human malignant tumors such as human lung cancer, gastric cancer, cancer of liver, uterine **cancer**, **colon cancer**, rectum **cancer**, rhinopharynx **cancer**, **thyroid** gland **cancer**, malignant melanoma, leukemia, and lymphoma, and attained a desired percentage surviving on the 35th day after the transplantation of human. . .

DETD . . . be selectively used as a therapeutic agent for human malignant tumors including gastric cancer, lung cancer, cancer of liver, uterine **cancer**, breast **cancer**, **colon cancer**, rectum **cancer**, and malignant melanoma.

DETD . . . be selectively used as a therapeutic agent for human malignant tumors including gastric cancer, lung cancer, cancer of liver, uterine **cancer**, breast **cancer**, **colon cancer**, rectum **cancer**, and malignant melanoma.

DETD . . . be selectively used as a therapeutic agent for human malignant tumors including gastric cancer, lung cancer, cancer of liver, uterine **cancer**, breast **cancer**, **colon cancer**, rectum **cancer**, and malignant melanoma.

DETD . . . be selectively used as a therapeutic agent for human malignant tumors including gastric cancer, lung cancer, cancer of liver, uterine **cancer**, breast **cancer**, **colon cancer**, rectum **cancer**, and malignant melanoma.

DETD These suppositories can be advantageously used as a therapeutic agent for human malignant **tumors** including **colon** and rectum **cancers**.

CLM What is claimed is:

. . . . member selected from the group consisting of sodium, potassium, calcium, magnesium and ammonium salts of 3-[4-hydroxy-3,5-bis(3-methyl-2-butenyl)phenyl]-2-propenoic acid, said human malignant **tumors** being **colon cancer**, rectum **cancer**, gastric **cancer**, **thyroid** gland **cancer**, lingual cancer, bladder cancer, choriocarcinoma, cancer of liver, uterine cancer, prostatic cancer, pharyngeal cancer, lung cancer, breast cancer, malignant melanoma, Kaposi sarcoma, brain tumor, neuroblastoma, ovarian tumor, testicular tumor, **osteosarcoma**, pancreatic **cancer**, **renal** carcinoma, hupernephroma, angioendothelioma, leukemia and lymphoma.

L14 ANSWER 4 OF 19 USPATFULL
AN 1998:7055 USPATFULL
TI Use of a melanoma differentiation associated gene (mda 7) for reversing a cancerous phenotype
IN Fisher, Paul B., Scarsdale, NY, United States
PA The Trustees of Columbia University in the City of New York, New York, NY, United States (U.S. corporation)
PI US 5710137 980120
AI US 96-696573 960816 (8)
DT Utility
EXNAM Primary Examiner: Marschel, Ardin H.
LREP White, John P.; Chan, Albert Wai-Kit
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 775
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method for reversing the cancerous phenotype of a cancer cell by introducing a nucleic acid having the melanoma differentiation associated gene (mda-7) into the cell under conditions that permit the expression of the gene so as to thereby reverse the cancerous phenotype of the cell. This invention also provides a method for reversing the cancerous phenotype of a cancer cell by introducing the gene product of the above-described gene into the cancerous cell so as to thereby reverse the cancerous phenotype of the cell. This invention also provides a pharmaceutical composition having an amount of a nucleic acid having the melanoma differentiation associated gene (mda-7) or the gene product of a melanoma differentiation associated gene (mda-7) effective to reverse the cancerous phenotype of a cancer cell and a pharmaceutically acceptable carrier.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . 14). This experimental strategy has been applied to human melanoma cells, induced to terminally differentiate by treatment with recombinant human **interferon .beta.** (IFN-.beta.) and mezerein (MEZ), resulting in the cloning of novel melanoma differentiation-associated (mda) genes not previously described in DNA data. . .
DETD . . . defects in growth control, and tumor cells often display abnormal patterns of cellular differentiation. The combination of recombinant human fibroblast **interferon** and the antileukemic agent mezerein corrects these abnormalities in cultured human melanoma cells resulting in irreversible growth arrest and terminal. . .
DETD . . . human cell types including HBL-100 (normal mammary epithelial), H0-1 and C8161 (melanoma), GBM-18 and T98G (glioblastoma multiforme) and Saos-2 (human **osteosarcoma**) were maintained under similar conditions. Early passage normal human mammary epithelial cells (HMEC; passages 10-12) were

obtained from Clonetics Corporation. . .
DETD . . . .+-. 12
T98G (Glioblastoma)
99 .+-. 9 32 .+-. 4(3.6)
115 .+-. 14
Saos-2 126 .+-. 22
35 .+-. 6(3.9)
138 .+-. 14
(**Osteosarcoma**)
Rat embryo fibroblast
CREF 60 .+-. 10
35 .+-. 5(1.7)
66 .+-. 7
(normal rat embryo)
CREF-ras 147 .+-. 16
25 .+-. 4(6.0)
151. . .
DETD . . . carcinoma (LS174T and SW480), nasopharyngeal carcinoma (HONE-1), prostate carcinoma (DU-145), melanoma (H0-1 and C8161), glioblastoma multiforme (GBM-18 and T98G) and **osteosarcoma** (Saos-2). As observed with HeLa cells, the average sizes of Hyg.sup.R colonies that form after transfection with mda-7 (S) constructs. . .
DETD To confirm the suppressive effect of mda-7 on cell growth, DU-145 human **prostate cancer** cells were engineered to express a DEX-inducible mda-7 gene. When DU-145 cl 6 or cl 7 cells [containing a DEX-inducible. . . 10.sup.-6 M DEX (data not shown). These data indicate that ectopic expression of mda-7 can directly alter cell growth in **prostate cancer** cells.
DETD . . . of mda-7 into the DU-145 human prostate carcinoma cell line that contains a mutated RB gene (38) and Saos-2 human **osteosarcoma** cells that do not express RB (or wild-type p53) results in an inhibition in colony formation (Table 1). Similarly, induction. . .

L14 ANSWER 5 OF 19 USPATFULL
AN 1998:4744 USPATFULL
TI Thioether conjugates
IN Willner, David, Hamden, CT, United States
Trail, Pamela A., Farmington, CT, United States
King, H. Dalton, Hamden, CT, United States
Hofstead, Sandra J., Middletown, CT, United States
Greenfield, Robert S., Wallingford, CT, United States
Braslawsky, Gary R., Glastonbury, CT, United States
PA Bristol-Myers Squibb Company, Princeton, NJ, United States (U.S. corporation)
PI US 5708146 980113
AI US 95-469840 950606 (8)
RLI Division of Ser. No. US 92-824951, filed on 23 Jan 1992, now patented, Pat. No. US 5622929
DT Utility
EXNAM Primary Examiner: Peselev, Elli
LREP Poor, Brian; Sorrentino, Joseph M.; Savitsky, Thomas R.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 18 Drawing Figure(s); 17 Drawing Page(s)
LN.CNT 2044
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided are drug/ligand compounds of Formula (I): ##STR1## (I) in which

D is a drug moiety;

n is an integer from 1 to 10;

p is an integer from 1 to 6;

Y is O or NH.sub.2.sup.+ Cl.sup.- ;

z is 0 or 1;

q is about 1 to about 10;

X is a ligand; and,

A is a Michael Addition Adduct.

In a preferred embodiment, the ligand is an immunoglobulin, preferably a chimeric antibody or fragment thereof. Also provided are formulations comprising as an active ingredient a compound of Formula (I), intermediates useful for preparing the compounds of Formula (I), processes for preparing the compounds of Formula (I), and methods for using the compounds of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DRWD FIG. 13 provides in vivo cytotoxic activity data for Adriamycin conjugates of relaxed Chimeric BR96 against RCA Human **Colon Tumors.**

DETD . . . example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-**interferon**, .**beta**.-**interferon**, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1. . .

DETD . . . Lung
G1, LuCa2,
Kyoizumi et al., Cancer Res., 45:3274
LuCa3, LuCa4
1985.
Small Cell Lung
TFS-2 Okabe et al., Cancer Res. 45:1930,
Cancer 1985.
Colon Cancer
11.285.14
G. Rowland, et al., Cancer Immunol.
14.95.55 Immunother., 19:1, 1985
NS-3a-22,NS-10
Z. Steplewski, et al., Cancer Res.,
NS-19-9,NS-33a
41:2723,. . . 91/00295, published January 10, 1991.
Breast Cancer
B6.2, B72.3
D. Colcher, et al., in Monoclonal Antibodies and Cancer, loc. cit. p. 121.
Osteogenic Sarcoma
791T/48, M. J. Embleton, ibid, p. 181
791T/36
Leukemia CALL 2 C. T. Teng, et al., Lancet, 1:01, 1982
anti-idiotype
. . . Invest.,
68:1331, 1981.
Prostrate Cancer
D83.21, P6.2,
J. J. Starling, et al., in Monoclonal
Turp-27 Antibodies and Cancer, loc. cit., p. 253
Renal Cancer

A6H, D5D P. H. Lange, et al., Surgery, 98:143, 1985.

DETD For animals bearing the RCA. **colon tumor**, therapy was initiated 15 days after tumor implant when the median tumor size was 75 mm.sup.3. The average TVDT for. . .

DETD TABLE V

Summary of Antitumor Activity of ChiBR96-ADM Thioether Conjugates Evaluated Against Established RCA Human **Colon Tumor** Xenografts

Conjugate ADM	ChiBR96 Dose (mg/kg).sup.a	Route	Log Cell Kill	% Tumor Regressions PR	% Tumor Regressions CR	No. of Cures	No. of Mice

---

ChiBR96-ADM-7.88	10 350. . .						

DETD In summary, the ChiBR96-ADM conjugate demonstrated antigen-specific antitumor activity in the RCA human **colon tumor** model. Cures and complete regressions of established RCA tumors were observed following the administration of ChiBR96-ADM conjugate at doses of. . .

L14 ANSWER 6 OF 19 USPATFULL
AN 97:122847 USPATFULL
TI Treatment for biological damage using a colony stimulating factor and a biological modifier
IN Zimmerman, Robert, Lafayette, CA, United States
Marafino, Jr., Benedict J., San Francisco, CA, United States
PA Chiron Corporation, Emeryville, CA, United States (U.S. corporation)
PI US 5702697 971230
AI US 95-457629 950601 (8)
RLI Continuation of Ser. No. US 94-289844, filed on 12 Aug 1994, now patented, Pat. No. US 5508031 which is a continuation of Ser. No. US 93-49070, filed on 16 Apr 1993, now abandoned which is a continuation of Ser. No. US 90-626975, filed on 12 Dec 1990, now abandoned which is a division of Ser. No. US 89-399386, filed on 25 Aug 1989, now patented, Pat. No. US 4985241 which is a continuation of Ser. No. US 87-113643, filed on 26 Oct 1987, now abandoned which is a continuation-in-part of Ser. No. US 86-933475, filed on 21 Nov 1986, now abandoned
DT Utility
EXNAM Primary Examiner: Ulm, John; Assistant Examiner: Mertz, Prema
LREP Gass, David A.; Savereide, Paul B.; Blackburn, Robert P.
CLMN Number of Claims: 32
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1705
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Damage to cells, tissue and other body parts in a mammalian host may be treated by using a colony stimulating factor in conjunction with at least one biological modifier, which may be a free radical scavenger or a metabolic inhibitor. The biological modifier is preferably uric acid, buthionine sulphoximine, vitamin C, aspirin, or nordihydroguaiaretic acid. Such a combination may be used to

. . . . . treat, for example, cancer, infectious diseases, and damage caused by radiation therapy, high oxygen tension, and chemotherapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Lymphokines and cytotoxins, such as interleukin-2, **interferon**-alpha, **interferon**-gamma, colony stimulating factor, and tumor necrosis factor, are proteins secreted by T cells and/or microphages upon activation by antigens or. . .

SUMM **Interferons** (IFN) constitute a group of naturally occurring proteins which are known to exhibit anti-viral, anti-tumor and immunoregulatory behavior. Two types. . . IFN have been identified based on differences in their observed biological properties and molecular structures: Type I and Type II. Beta-**interferon** (IFN-.beta.) is a Type I IFN which can be induced in fibroblasts by viral challenge and contains about 165 amino. . .

SUMM . . . Kreuzes)) or with augmentation of natural killer activity (Svedersky et al., J. Immunol. (1984), 133:714-718 and Shalaby et al., J. **Interferon** Res. (1985), 5:571-581). In addition, U.S. Statutory Invention Reg. No. H22, published Feb. 4, 1986 to Creasey et al., discloses. . . in combination therapy of certain breast cancer and myeloma cell lines using synergistically effective amounts of 5-fluorouracil and human recombinant beta-**interferon**. Furthermore, enhanced anti-tumor activity has been observed using IFN-.gamma. in combination with TNF and chemotherapeutic agents. Svedersky et al., Internl.. . .

SUMM . . . foreign agents such as pathogens in the cell. Examples of such lymphokines and cytotoxins include, but are not limited to, **interferons** (e.g., **interferon**-alpha, (IFN-.alpha.), **interferon-beta**, (IFN-.beta.), and **interferon**-gamma, (IFN-.alpha.)), interleukins (e.g., interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-3 (IL-3), and interleukin-4 (IL-4)), tumor necrosis factor-alpha (TNF-.alpha.), tumor necrosis factor-beta (TNF-.beta.). . . inhibitory activity factor (MIF), macrophage-activating factor (MAF), NK cell activating factor, T cell replacing factor, leukocyte-inhibitory factor (LIF), other lymphotoxins, **osteoclast**-activating factor (OAF), soluble immune response suppressor (SIRS), growth-stimulating factor, a monocyte growth factor, etc. Preferably, the lymphokine or cytotoxin is an interleukin (more preferably IL-2), an **interferon** (more preferably IFN-.beta.), TNF-.alpha. or -.beta., or a colony stimulating factor (more preferably CSF-1). The most preferred herein is TNF-.alpha..

SUMM . . . term "cancer" as used in the above definition refers to any neoplastic disorder, including such cellular disorders as, for example, **renal** cell **cancer**, Kaposi's sarcoma, chronic leukemia, breast cancer, sarcoma, ovarian carcinoma, rectal cancer, throat **cancer**, melanoma, **colon cancer**, bladder **cancer**, mastocytoma, lung cancer and gastrointestinal or stomach cancer. Preferably, the **cancer** is **colon cancer**, melanoma, **renal** cell **cancer**, sarcoma, lung cancer, adenocarcinoma, or breast cancer.

SUMM The typical dosage level of **interferon** (especially INF-.beta.) in humans ranges from about 100 units to one billion units/m.sup.2. Preferably, IFN-.beta. is administered to humans in. . .

DETD . . . anti-tumor effect in animals and humans. The preclinical response of TNF alone correlated with a clinical response of TNF to **colon cancer**.

DETD . . . Correlate With TNF Resistance In Vivo

.mu.M Total

Tumor Line	Glutathione Equivalents/ 10.sup.6 cells	% Tumor Growth Inhibition.sup.a
PAN-D2 (mouse **tumor**)	484 .+-. 90	0
HT29 (human **colon** tumor)	308 .+-. 131	9
P815 (mouse tumor)	305 .+-. 197	20
P388 (mouse tumor)	280 .+-. 150	15
B-16 (mouse tumor)	180 .+-.. . .	

L14 ANSWER 7 OF 19 USPATFULL
AN 97:89066 USPATFULL
TI Purification of human myelomonocyte **interferon** gamma with an immobilized antibody
IN Kurimoto, Masashi, Okayama, Japan
Mitsuhashi, Masakazu, Okayama, Japan
PA Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Okayama, Japan (non-U.S. corporation)
PI US 5672692 970930
AI US 96-625369 960401 (8)
RLI Division of Ser. No. US 95-476040, filed on 7 Jun 1995, now patented, Pat. No. US 5554515 which is a division of Ser. No. US 94-336224, filed on 7 Nov 1994, now patented, Pat. No. US 5518899 which is a division of Ser. No. US 93-62323, filed on 17 May 1993, now patented, Pat. No. US 5362490 which is a continuation of Ser. No. US 91-658740, filed on 22 Feb 1991, now abandoned which is a continuation-in-part of Ser. No. US 87-78005, filed on 21 Jul 1987, now abandoned And Ser. No. US 89-379318, filed on 13 Jul 1989, now abandoned
PRAI JP 86-176266 860725
JP 87-125777 870525
JP 88-184069 880723
DT Utility
EXNAM Primary Examiner: Naff, David M.
LREP Browdy and Neimark
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1153
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A human myelomonocyte **interferon**-gamma having a novel polypeptide and carbohydrate chain structure is produced by propagation of an established human myelomonocyte in vitro or after being implanted in a non-human warm-blooded animal or in a diffusion chamber placed inside or outside the body of the animal. The human myelomonocyte may be contacted with an inducer during propagation. A monoclonal antibody specific to the human myelomonocyte **interferon**-gamma is produced by immunizing a non-human warm-blooded animal with purified human myelomonocyte **interferon**-gamma as an antigen, recovering an antibody producing cell from the animal and fusing the cell with a myeloma cell to produce a hybrid capable of producing the monoclonal antibody. The human myelomonocyte **interferon**-gamma can be purified by chromatography with an immobilized anti-human myelomonocyte **interferon**-gamma antibody such as the monoclonal antibody. The human myelomonocyte **interferon** -gamma can be used as a prophylactic and therapeutic agent for human **interferon**-gamma susceptive diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Purification of human myelomonocyte **interferon** gamma with an immobilized antibody

AB A human myelomonocyte **interferon**-gamma having a novel polypeptide and carbohydrate chain structure is produced by propagation of an established human myelomonocyte in vitro or. . . animal. The human myelomonocyte may be contacted with an inducer during propagation. A monoclonal antibody specific to the human myelomonocyte **interferon**-gamma is produced by immunizing a non-human warm-blooded animal with purified human myelomonocyte **interferon**-gamma as an antigen, recovering an antibody producing cell from the animal and fusing the cell with a myeloma cell to produce a hybrid capable of producing the monoclonal antibody. The human myelomonocyte **interferon**-gamma can be purified by chromatography with an immobilized anti-human myelomonocyte **interferon**-gamma antibody such as the monoclonal antibody. The human myelomonocyte **interferon**-gamma can be used as a prophylactic and therapeutic agent for human **interferon**-gamma susceptive diseases.

SUMM The present invention relates to a novel human myelomonocyte **interferon**-gamma, a process to prepare said **interferon**-gamma, and its use.

SUMM More particularly, the present invention relates to a novel human myelomonocyte **interferon**-gamma, and a process for preparing said **interferon**-gamma, characterized by allowing an established human myelomonocyte capable of producing myelomonocyte **interferon**-gamma to produce said **interferon**-gamma, and recovering the accumulation; a process to prepare a monoclonal anti-**interferon**-gamma antibody using the same; and a method for purifying said **interferon**-gamma using the monoclonal antibody, as well as to a prophylactic and therapeutic agent for **interferon**-gamma susceptive disease containing the human myelomonocyte **interferon**-gamma as an effective ingredient.

SUMM As described in Shigeyasu Kobayashi, "**Interferon**", published by Kodansha Co., Ltd., Tokyo, Japan (1975), D. A. J. Tyrrell, "**Interferon** and its Clinical Potential", published by William Heinemann Medical Books Ltd., London (1976), and Protein, Nucleic Acid and Enzyme, Vol.21, No.4, pp.245-333 (1976), **interferon** is a name to designate glycoproteins that are extracellularly inducible in viable cell by subjecting it to the action of an **interferon inducer**, for example, virus, bacterium, protozoon, **rickettsia**, nucleic acid, endotoxin and polysaccharide, as well as having an activity of nonspecifically inhibiting viral growth.

SUMM This activity has rendered **interferons** since the discovery a potential prophylactic and therapeutic agent for vital diseases. Recent studies revealed that **interferons** exert an antioncotic activity on vital tumors, as well as on nonviral tumors. Because of the activity, the development of pharmaceuticals using **interferons** is in great expectation.

SUMM **Interferons** include **interferon**-alpha (or leukocyte **interferon**), **interferon-beta** (or fibroblast **interferon**), and **interferon**-gamma (or immune **interferon**). Preparation of **interferon**-alpha and **interferon-beta** has been established by using leukocyte and fibroblast cell. Recently, pharmaceuticals incorporated with these **interferons** have been commercialized.

SUMM Respective **interferon** will hereinafter be abbreviated as "IFN-alpha", "IFN-beta" and "IFN-gamma" occasionally with the prefix "Hu" representing human origin.

DETD . . . as epidemic conjunctivitis, herpetic keratitis, influenza, rubella, serum hepatitis, and acquired immune deficiency syndrome (AIDS); and nonviral diseases including malignant **tumors** such as **colon** carcinoma, lung carcinoma, liver carcinoma and **osteosarcoma**, and immunopathies including atopic allergy, myoasthenia, collagenosis, pernicious anemia, articular rheumatism, and systemic lupus erythematosus.

DETD . . . and therapeutic agent for vital disease such as those in small and large intestines, as well as that for malignant **tumors** such as **colon** carcinoma and liver carcinoma, and immunopathies such as atopic allergy, pernicious anemia, articular rheumatism, and systemic lupus erythematosus.

CLM What is claimed is:

1. A method for purifying a human myelomonocyte **interferon**-gamma, comprising: propagating an established human myelomonocyte which produces human myelomonocyte **interferon**-gamma; and recovering the human myelomonocyte **interferon**-gamma by column chromatography using an antibody specific to human myelomonocyte **interferon**-gamma.

2. The method of claim 1, wherein said established human myelomonocyte is obtained by: implanting an established human myelomonocyte capable of producing human myelomonocyte **interferon**-gamma in a non-human warm-blooded animal, or inoculating the established human myelomonocyte in a diffusion chamber placed inside or outside the. . .

3. The method of claim 1, wherein said antibody specific to human myelomonocyte **interferon**-gamma is obtained by: propagating an established human myelomonocyte which produces myelomonocyte **interferon**-gamma; recovering and purifying the **interferon**-gamma produced by said human myelomonocyte; immunizing a non-human warm-blooded animal using the recovered and purified human myelomonocyte **interferon**-gamma as an antigen; recovering an antibody producing cell from the animal; fusing said antibody producing cell with a myeloma cell. . . hybrid cells; selecting from said hybrid cells a hybrid cell capable of producing a monoclonal antibody specific to human myelomonocyte **interferon**-gamma; and culturing the hybrid cell to produce said monoclonal antibody specific to human myelomonocyte **interferon**-gamma.

L14 ANSWER 8 OF 19 USPATFULL

AN 97:83609 USPATFULL

TI Treatment for biological damage using tumor necrosis factor and a free-radical scavenger

IN Zimmerman, Robert, Lafayette, CA, United States
Marafino, Jr., Benedict J., San Francisco, CA, United States

PA Chiron Corporation, Emeryville, CA, United States (U.S. corporation)

PI US 5667776 970916

AI US 95-456947 950601 (8)

RLI Continuation of Ser. No. US 94-289844, filed on 12 Aug 1994, now patented, Pat. No. US 5508031 which is a continuation of Ser. No. US 93-49070, filed on 16 Apr 1993, now abandoned which is a continuation of Ser. No. US 90-626975, filed on 12 Dec 1990, now abandoned which is a division of Ser. No. US 89-399386, filed on 25 Aug 1989, now patented, Pat. No. US 4985241 which is a continuation of Ser. No. US 87-113643, filed on 26 Oct 1987, now abandoned which is a continuation-in-part of Ser. No. US 86-933475, filed on 21 Nov 1986, now abandoned

DT Utility

EXNAM Primary Examiner: Ulm, John; Assistant Examiner: Mertz, Prema

LREP Gass, David A.; Savereide, Paul B.; Blackburn, Robert P.

CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1648
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Damage to cells, tissue and other body parts in a mammalian host may be treated by using a tumor necrosis factor in conjunction with at least one biological modifier, which may be a free radical scavenger or a metabolic inhibitor. The biological modifier is preferably uric acid, buthionine sulphoximine, vitamin C, aspirin, or nordihydroguaiaretic acid. Such a combination may be used to treat, for example, cancer, infectious diseases, and damage caused by radiation therapy, high oxygen tension, and chemotherapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM Lymphokines and cytotoxins, such as interleukin-2, **interferon**-alpha, **interferon**-gamma, colony stimulating factor, and tumor necrosis factor, are proteins secreted by T cells and/or macrophages upon activation by antigens or. . .

SUMM **Interferons** (IFN) constitute a group of naturally occurring proteins which are known to exhibit anti-viral, anti-tumor and immunoregulatory behavior. Two types. . . IFN have been identified based on differences in their observed biological properties and molecular structures: Type I and Type II. Beta-**interferon** (IFN-.beta.) is a Type I IFN which can be induced in fibroblasts by viral challenge and contains about 165 amino. . .

SUMM . . . Kreuzes)) or with augmentation of natural killer activity (Svedersky et al., J. Immunol. (1984), 133:714-718 and Shalaby et al., J. **Interferon** Res. (1985), 5:571-581). In addition, U.S. Statutory Invention Reg. No. H22, published Feb. 4, 1986 to Creasey et al., discloses. . . in combination therapy of certain breast cancer and myeloma cell lines using synergistically effective amounts of 5-fluorouracil and human recombinant beta-**interferon**. Furthermore, enhanced anti-tumor activity has been observed using IFN-.gamma. in combination with TNF and chemotherapeutic agents. Svedersky et al., Internl.. . .

DETD . . . foreign agents such as pathogens in the cell. Examples of such lymphokines and cytotoxins include, but are not limited to, **interferons** (e.g., **interferon**-alpha, (IFN-.alpha.), **interferon-beta**, (IFN-.beta.), and **interferon**-gamma, (IFN-.alpha.)), interleukins (e.g., interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-3 (IL-3), and interleukin-4 (IL-4)), tumor necrosis factor-alpha (TNF-.alpha.), tumor necrosis factor-beta (TNF-.beta.). . . inhibitory activity factor (MIF), macrophage-activating factor (MAF), NK cell activating factor, T cell replacing factor, leukocyte-inhibitory factor (LIF), other lymphotoxins, **osteoclast**-activating factor (OAF), soluble immune response suppressor (SIRS), growth-stimulating factor, a monocyte growth factor, etc. Preferably, the lymphokine or cytotoxin is an interleukin (more preferably IL-2), an **interferon** (more preferably IFN-.beta.), TNF-.alpha. or -.beta., or a colony stimulating factor (more preferably CSF-1). The most preferred herein is TNF-.alpha..

DETD . . . term "cancer" as used in the above definition refers to any neoplastic disorder, including such cellular disorders as, for example, **renal** cell **cancer**, Kaposi's sarcoma, chronic leukemia, breast cancer, sarcoma, ovarian carcinoma, rectal cancer, throat **cancer**, melanoma, **colon cancer**, bladder **cancer**, mastocytoma, lung cancer and gastrointestinal or stomach cancer. Preferably, the **cancer** is **colon cancer**, melanoma, **renal** cell **cancer**, sarcoma, lung cancer,

adenocarcinoma, or breast cancer.

DETD The typical dosage level of **interferon** (especially INF-.beta.) in humans ranges from about 100 units to one billion units/m.sup.2. Preferably, IFN-.beta. is administered to humans in. . .

DETD . . . anti-tumor effect in animals and humans. The preclinical response of TNF alone correlated with a clinical response of TNF to **colon cancer**.

DETD . . . Correlate With TNF Resistance In Vivo

Tumor Line	.mu.M Total Glutathione Equivalents /10.sup.6 cells	% Tumor Growth Inhibition.sup.a
PAN-02 (mouse **tumor**)	484 .+-. 90	0
HT29 (human **colon** tumor)	308 .+-. 131	9
P815 (mouse tumor)	305 .+-. 197	20
P388 (mouse tumor)	280 .+-. 150	15
B-16 (mouse tumor)	180 .+-.. . .	

L14 ANSWER 9 OF 19 USPATFULL

AN 97:33724 USPATFULL

TI Thioether conjugates

IN Willner, David, Hamden, CT, United States
Trail, Pamela A., Farmington, CT, United States
King, H. Dalton, Hamden, CT, United States
Hofstead, Sandra J., Middletown, CT, United States
Greenfield, Robert S., Wallingford, CT, United States
Braslawsky, Gary R., Glastonbury, CT, United States

PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)

PI US 5622929 970422

AI US 92-824951 920123 (7)

DT Utility

EXNAM Primary Examiner: Peselev, Elli

LREP Bristol-Myers Squibb Co.

CLMN Number of Claims: 52

ECL Exemplary Claim: 6

DRWN 18 Drawing Figure(s); 17 Drawing Page(s)

LN.CNT 2212

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided are drug/ligand compounds of Formula (I): ##STR1## in which D is a drug moiety;

n is an integer from 1 to 10;

p is an integer from 1 to 6;

Y is O or NH.sub.2.sup.+ Cl.sup.- ;

z is 0 or 1;

q is about 1 to about 10;

X is a ligand; and,

A is a Michael Addition Adduct.

In a preferred embodiment, the ligand is an immunoglobulin, preferably a chimeric antibody or fragment thereof. Also provided are formulations comprising as an active ingredient a compound of Formula (I), intermediates useful for preparing the compounds of Formula (I), processes for preparing the compounds of Formula (I), and methods for using the compounds of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DRWD FIG. 13 provides in vivo cytotoxic activity data for Adriamycin conjugates of relaxed Chimeric BR96 against RCA Human **Colon Tumors.**

DETD . . . example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-**interferon**, .**beta**.-**interferon**, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1. . .

DETD . . . G1, LuCa2, Kyoizumi et al., Cancer Res., LuCa3, 45:3274 1985.
LuCa4

Small Cell
TFS-2 Okabe et al., Cancer Res.
Lung Cancer 45:1930, 1985.

Colon Cancer
11.285.14 G. Rowland, et al., Cancer
14.95.55 Immunol. Immunother., 19:1, 1985
NS-3a-22, Z. Steplewski, et al., Cancer
NS-10 Res., 41:2723,. . . 91/00295, published January 10, 1991.

Breast Cancer
B6.2, B72.3
D. Colcher, et al., in Monoclonal Antibodies and Cancer, loc. cit. p. 121.

Osteogenic
791T/48, M. J. Embleton, ibid, p. 181
Sarcoma 791T/36
Leukemia CALL 2 C. T. Teng, et al., Lancet, 1:01, 1982
anti-idiotype
R.. . . Clin. Invest., 68:1331, 1981.
Prostrate D83.21, P6.2,
J. J. Starling, et al., in
Cancer Turp-27 Monoclonal Antibodies and Cancer, loc. cit., p. 253

Renal Cancer
A6H, D5D P. H. Lange, et al., Surgery, 98:143, 1985.

DETD For animals bearing the RCA **colon tumor**, therapy was initiated 15 days after tumor implant when the median tumor size was 75 mm.sup.3. The average TVDT for. . .

DETD TABLE V

Summary of Antitumor Activity of ChiBR96-ADM Thioether Conjugates Evaluated
Against Established RCA Human **Colon Tumor** Xenografts

Dose (mg/kg).sup.a	Log Cell % Tumor	No.

Regressions
of
Conjugate ADM ChiBR96
Route
Kill
PR CR Cures
Mice

ChiBR96-ADM-7.88
10 350. . .
DETD In summary, the ChiBR96-ADM conjugate demonstrated antigen-specific antitumor activity in the RCA human **colon tumor** model. Cures and complete regressions of established RCA tumors were observed following the administration of ChiBR96-ADM conjugate at doses of. . .

L14 ANSWER 10 OF 19 USPATFULL
AN 97:16169 USPATFULL
TI Thioether conjugates
IN Willner, David, Hamden, CT, United States
Trail, Pamela A., Farmington, CT, United States
King, H. Dalton, Hamden, CT, United States
Hofstead, Sandra J., Middletown, CT, United States
Greenfield, Robert S., Wallingford, CT, United States
Braslawsky, Gary R., Glastonbury, CT, United States
PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)
PI US 5606017 970225
AI US 95-468162 950606 (8)
RLI Division of Ser. No. US 92-824951, filed on 23 Jan 1992
DT Utility
EXNAM Primary Examiner: Peselev, Elli
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 18 Drawing Figure(s); 17 Drawing Page(s)
LN.CNT 2095
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided are drug/ligand compounds of Formula (I): ##STR1## in which D is a drug moiety;

n is an integer from 1 to 10;

p is an integer from 1 to 6;

Y is O or NH.sub.2.sup.+ Cl.sup.- ;

z is 0 or 1;

q is about 1 to about 10;

X is a ligand; and,

A is a Michael Addition Adduct.

In a preferred embodiment, the ligand is an immunoglobulin, preferably a chimeric antibody or fragment thereof. Also provided are formulations comprising as an active ingredient a compound of Formula (I), intermediates useful for preparing the compounds of Formula (I), processes for preparing the compounds of Formula (I), and methods for using the compounds of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DRWD FIG. 13 provides in vivo cytotoxic activity data for Adriamycin conjugates of relaxed Chimeric BR96 against RCA Human

Colon Tumors.

DETD . . . example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-**interferon**, .**beta**.-**interferon**, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1. . .

DETD . . . Lung

	G1, LuCa2,	Kyoizumi et al., Cancer Res., 45:3274
	LuCa3, LuCa4	1985.
Small Cell Lung		
	TFS-2	Okabe et al., Cancer Res. 45:1930,
cancer		1985.
Colon Cancer		
	11.285.14	G. Rowland, et al., Cancer Immunol.
	14.95.55	Immunother., 19:1, 1985
	NS-3a-22, NS-10	Z. Steplewski, et al., Cancer Res.,
	NS-19-9,. . .	91/00295, published January 10, 1991.
Breast Cancer		
	B6.2, B72.3	D. Colcher, et al., in Monoclonal Antibodies and Cancer, loc. cit. p. 121.
Osteogenic Sarcoma		
	791T/48, 791T/36	M. J. Embleton, ibid, p. 181
Leukemia	CALL 2	C. T. Teng, et al., Lancet, 1:01, 1982
	anti-idiotype	
. . .	Invest.,	68:1331, 1981.
Prostrate Cancer		
	D83.21, P6.2, Turp-27	J. J. Starling, et al., in Monoclonal Antibodies and Cancer, loc. cit., p. 253
Renal Cancer		
	A6H, DSD	P. H. Lange, et al., Surgery, 98:143, 1985.

DETD For animals bearing the RCA **colon tumor**, therapy was initiated 15 days after tumor implant when the median tumor size was 75 mm.sup.3. The average TVDT for. . .

DETD TABLE V

Summary of Antitumor Activity of ChiBR96-ADM Thioether Conjugates Evaluated Against Established RCA Human **Colon Tumor** Xenografts

Conjugate	Dose (mg/kg).sup.a	Route	Log Kill	% Tumor Cell Regressions PR	% Tumor Cell Regressions CR	No. of Cure Mice
ADM ChiBR96						

ChiBR96-ADM-7.88
10 350. . .
DETD In summary, the ChiBR96-ADM conjugate demonstrated antigen-specific antitumor activity in the RCA human **colon tumor** model. Cures and complete regressions of established RCA tumors were observed following the administration of ChiBR96-ADM conjugate at doses of. . .

L14 ANSWER 11 OF 19 USPATFULL
AN 96:82590 USPATFULL
TI Preparation of a monoclonal antibody specific to human myelomonocyte **interferon**-gamma
IN Kurimoto, Masashi, Okayama, Japan
Mitsuhashi, Masakazu, Okayama, Japan
PA Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Okayama, Japan (non-U.S. corporation)
PI US 5554515 960910
AI US 95-476040 950607 (8)
RLI Division of Ser. No. US 94-336224, filed on 7 Nov 1994 which is a division of Ser. No. US 93-62323, filed on 17 May 1993, now patented, Pat. No. US 5362490 which is a continuation of Ser. No. US 91-658740, filed on 22 Feb 1991, now abandoned which is a continuation-in-part of Ser. No. US 87-78005, filed on 21 Jul 1987, now abandoned And a continuation-in-part of Ser. No. US 89-379318, filed on 13 Jul 1989, now abandoned
PRAI JP 86-176266 860725
JP 87-125777 870525
JP 88-184069 880723
DT Utility
EXNAM Primary Examiner: Naff, David M.
LREP Browdy and Neimark
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1141
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A human myelomonocyte **interferon**-gamma having a novel polypeptide and carbohydrate chain structure is produced by propagation of an established human myelomonocyte in vitro or after being implanted in a non-human warm-blooded animal or in a diffusion chamber placed inside or outside the body of the animal. The human myelomonocyte may be contacted with an inducer during propagation. A monoclonal antibody specific to the human myelomonocyte **interferon**-gamma is produced by immunizing a non-human warm-blooded animal with purified human myelomonocyte **interferon**-gamma as an antigen, recovering an antibody producing cell from the animal and fusing the cell with a myeloma cell to produce a hybrid capable of producing the monoclonal antibody. The human myelomonocyte **interferon**-gamma can be purified by chromatography with an anti-human myelomonocyte **interferon**-gamma antibody such as the monoclonal antibody. The human myelomonocyte **interferon**-gamma can be used as a prophylactic and therapeutic agent for human **interferon**-gamma susceptive diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Preparation of a monoclonal antibody specific to human myelomonocyte **interferon**-gamma
AB A human myelomonocyte **interferon**-gamma having a novel polypeptide and carbohydrate chain structure is produced by propagation of an established human myelomonocyte in vitro or. . . animal. The human myelomonocyte may be contacted with an inducer during propagation. A monoclonal antibody specific to the human myelomonocyte **interferon**-gamma is produced by

immunizing a non-human warm-blooded animal with purified human myelomonocyte **interferon**-gamma as an antigen, recovering an antibody producing cell from the animal and fusing the cell with a myeloma cell to produce a hybrid capable of producing the monoclonal antibody. The human myelomonocyte **interferon**-gamma can be purified by chromatography with an anti-human myelomonocyte **interferon**-gamma antibody such as the monoclonal antibody. The human myelomonocyte **interferon**-gamma can be used as a prophylactic and therapeutic agent for human **interferon**-gamma susceptive diseases.

SUMM The present invention relates to a novel human myelomonocyte **interferon**-gamma, a process to prepare said **interferon**-gamma, and its use.

SUMM More particularly, the present invention relates to a novel human myelomonocyte **interferon**-gamma, and a process for preparing said **interferon**-gamma, characterized by allowing an established human myelomonocyte capable of producing myelomonocyte **interferon**-gamma to produce said **interferon**-gamma, and recovering the accumulation; a process to prepare a monoclonal anti-**interferon**-gamma antibody using the same; and a method for purifying said **interferon**-gamma using the monoclonal antibody, as well as to a prophylactic and therapeutic agent for **interferon**-gamma susceptive disease containing the human myelomonocyte **interferon**-gamma as an effective ingredient.

SUMM As described in Shigeyasu Kobayashi, "**Interferon**", published by Kodansha Co., Ltd., Tokyo, Japan (1975), D. A. J. Tyrrell, "**Interferon** and its Clinical Potential", published by William Heinemann Medical Books Ltd., London (1976), and Protein, Nucleic Acid and Enzyme, Vol. 21, No. 4, pp. 245-333 (1976), **interferon** is a name to designate glycoproteins that are extracellularly inducible in viable cell by subjecting it to the action of an **interferon inducer**, for example, virus, bacterium, protozoon, **rickettsia**, nucleic acid, endotoxin and polysaccharide, as well as having an activity of nonspecifically inhibiting viral growth.

SUMM This activity has rendered **interferons** since the discovery a potential prophylactic and therapeutic agent for viral diseases. Recent studies revealed that **interferons** exert an antioncotic activity on viral tumors, as well as on nonviral tumors. Because of the activity, the development of pharmaceuticals using **interferons** is in great expectation.

SUMM **Interferons** include **interferon**-alpha (or leukocyte **interferon**), **interferon-beta** (or fibroblast **interferon**), and **interferon**-gamma (or immune **interferon**). Preparation of **interferon**-alpha and **interferon-beta** has been established by using leukocyte and fibroblast cell. Recently, pharmaceuticals incorporated with these **interferons** have been commercialized.

SUMM Respective **interferon** will hereinafter be abbreviated as "IFN-alpha", "IFN-beta" and "IFN-gamma" occasionally with the prefix "Hu" representing human origin.

DETD . . . as epidemic conjunctivitis, herpetic keratitis, influenza, rubella, serum hepatitis, and acquired immune deficiency syndrome (AIDS); and nonviral diseases including malignant **tumors** such as **colon** carcinoma, lung carcinoma, liver carcinoma and **osteosarcoma**, and immunopathies including atopic allergy, myoasthenia, collagenosis, pernicious anemia, articular rheumatism, and systemic lupus erythematosus.

DETD . . . and therapeutic agent for viral disease such as those in small and large intestines, as well as that for malignant **tumors** such as **colon** carcinoma and liver

carcinoma, and immunopathies such as atopic allergy, pernicious anemia, articular rheumatism, and systemic lupus erythematosus.

CLM What is claimed is:

1. A process for preparing a monoclonal antibody specific to human myelomonocyte **interferon**-gamma, comprising: propagating an established human myelomonocyte which produces myelomonocyte **interferon**-gamma; recovering and purifying the **interferon**-gamma produced by said human myelomonocyte; immunizing a non-human warm-blooded animal using the recovered and purified human myelomonocyte **interferon**-gamma as an antigen; recovering an antibody producing cell from the animal; fusing said antibody producing cell with a myeloma cell. . . to produce hybrid cells; selecting from said hybrid cells a hybrid cell capable of producing antibody specific to human myelomonocyte **interferon**-gamma; and culturing the hybrid cell to produce said monoclonal antibody specific to human myelomonocyte **interferon**-gamma.

. . . claim 1, wherein said established human myelomonocyte is obtained by: implanting an established human myelomonocyte capable of producing human myelomonocyte **interferon**-gamma in a non-human warm-blooded animal, or inoculating the established human myelomonocyte in a diffusion chamber placed inside or outside the. . .

L14 ANSWER 12 OF 19 USPATFULL
AN 96:63033 USPATFULL
TI Diagnostic and prognostic methods for solid non-lymphoid tumors and their metastases
IN Barbera-Guillem, Emilio, Apt. 209B Chestnut Ridge, Amherst, NY, United States 14228
Cohen, Stefan A., 24 Wagon Wheel Dr., East Amherst, NY, United States 14051
PI US 5536642 960716
AI US 93-118969 930909 (8)
DT Utility
EXNAM Primary Examiner: Scheiner, Toni R.
LREP Hodgson, Russ, Andrews, Woods & Goodyear
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 1132
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to the measurement of cell-associated interleukin-2 receptor .alpha. (IL-2R.alpha.) expression in solid non-lymphoid tumors, and the use of such measurement In prognosing the metastatic potential of the tumor, diagnosing the metastatic localization of non-lymphoid tumor, and aiding the monitoring of efficacy of anticancer therapy against metastatic cells of non-lymphoid tumor. The present invention also relates to the use of T-cell receptor (tumor specific TCR.beta. idiotype) in monitoring the efficacy of anticancer therapy against non-lymphoid tumors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . 39:3-21); (c) treatment is more complex than simple surgical excision of the primary tumor; (d) systemic therapy for metatstatic non-lymphoid **tumors**, such as **renal** cell carcinoma (Rosenberg et al., 1985, N. Engl. J. Med. 313:1485-1492), remains ineffective with little survival advantage; and (e) not. . .
SUMM . . . of flavone-8-acetic acid and recombinant IL-2; U.S. Patent No. 5,098,702 to Zimmerman et al. disclosing a combination of IL-2 and/or **Interferon-.beta.** and tumor necrosis factor against tumor cells; U.S. Pat. No. 4,939,093 to

DETD				. . .	Colon Carcinoma
		High.sup.(1)			
			ND	+	100%*
B16F10	Melanoma	High	High	+	100%*
B16F10LM (B)					
	Liver met. microfoci				
		Metastasis			
			ND	ND	100%*
	Melanoma				
Human **Tumors**					
SW480E	**Colon** Carcinoma				
		Low.sup.(2)			
			Low	-	<1%*
	Prim. Tum. (CL)				
SW480	Colon Carcinoma				
		Low.sup.(2)			
			Low	+	10%*
	Prim. Tum. (CL)				
SW480R	Colon Carcinoma				
		High.sup.(2)			
. . .	Carcinoma (CL)				
		ND	ND	-	50%*
HepG2	Hepatoma (CL)				
		ND	ND	-	75%*
LS174T	Colonic Carcinoma (CL)				
		ND	ND	-	50%*
VA59P (B)					
	Osteo Sarcoma				
		Prim.Tum.			
			Low	ND	
VA59M (B)					
	Limph.N.Met. (VA59P)				
		Metastatis			
			High	ND	
BICO5P (B)					
	Colon Carcinoma				
		Prim.Tum.			
			ND	ND	5%**
BIC52MH (B)					
	Liver Met.(BIO5P)				

. . .			
DETD		. . .	+
E8	colonic carcinoma		+
A549	lung carcinoma		-
SEPPLO	renal carcinoma		-
HELA	cervix carcinoma		-
HL-60	promyelocytic leukemia		+
HepG2	hepatoma		-
Primary Tumor Biopsies			
BVal50	**osteosarcoma**		-
BVal21	**osteosarcoma**		+
BVal84	**osteosarcoma**		+
BVal8	**osteosarcoma**		+
BVal46	**osteosarcoma**		+
BVal76	**osteosarcoma**		-
BVal102	**osteosarcoma**		+
BVal56	**osteosarcoma**		+
BVal88	**osteosarcoma**		+
BVal100	**osteosarcoma**		+
BVal154	**osteosarcoma**		+
BVal-C1594	rethinoblastoma		+
BVal-C-700	rethinoblastoma		+

L14 ANSWER 13 OF 19 USPATFULL
AN 96:43552 USPATFULL
TI Preparation of human myelomonocyte **interferon**-gamma
IN Kurimoto, Masashi, Okayama, Japan
Mitsuhashi, Masakazu, Okayama, Japan
PA Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Oakyama, Japan (non-U.S. corporation)
PI US 5518899 960521
AI US 94-336224 941107 (8)
RLI Division of Ser. No. US 93-62323, filed on 17 May 1993, now patented, Pat. No. US 5362490 which is a continuation of Ser. No. US 91-658740, filed on 22 Feb 1991, now abandoned which is a continuation-in-part of Ser. No. US 87-78005, filed on 21 Jul 1987, now abandoned And a continuation-in-part of Ser. No. US 89-379318, filed on 13 Jul 1989, now abandoned
PRAI JP 86-176266 860725
JP 87-125777 870525
JP 88-184069 880723
DT Utility
EXNAM Primary Examiner: Naff, David M.
LREP Browdy and Neimark
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1146
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a novel human **interferon**-gamma derived from an established human myelomonocyte, a process to prepare said **interferon**-gamma, and its use. The human myelomonocyte **interferon**-gamma has a novel polypeptide and carbohydrate chain structure, and it is effective in preventing and treating viral diseases, malignant tumors and immunopathies alone or in combination with other lymphokine and/or chemotherapeutic. The human myelomonocyte **interferon**-gamma may be produced by culturing an established human myelomonocyte on a culture medium in vitro. Alternatively, an established human myelomonocyte is implanted in a non-human warm-blooded animal or in a diffusion chamber placed inside or outside the body of the animal, and then allowed to proliferate while receiving nutrient body fluid from the animal. The human myelomonocyte may be contacted with an inducer during propagation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Preparation of human myelomonocyte **interferon**-gamma
AB The present invention relates to a novel human **interferon**-gamma derived from an established human myelomonocyte, a process to prepare said **interferon**-gamma, and its use. The human myelomonocyte **interferon**-gamma has a novel polypeptide and carbohydrate chain structure, and it is effective in preventing and treating viral diseases, malignant tumors and immunopathies alone or in combination with other lymphokine and/or chemotherapeutic. The human myelomonocyte **interferon**-gamma may be produced by culturing an established human myelomonocyte on a culture medium in vitro. Alternatively, an established human myelomonocyte. . .
SUMM The present invention relates to a novel human myelomonocyte **interferon**-gamma, a process to prepare said **interferon**-gamma, and its use.
SUMM More particularly, the present invention relates to a novel human myelomonocyte **interferon**-gamma, and a process for preparing said **interferon**-gamma, characterized by allowing an established human myelomonocyte capable of producing

myelomonocyte **interferon**-gamma to produce said **interferon**-gamma, and recovering the accumulation; a process to prepare a monoclonal anti-**interferon**-gamma antibody using the same; and a method for purifying said **interferon**-gamma using the monoclonal antibody, as well as to a prophylactic and therapeutic agent for **interferon**-gamma susceptive disease containing the human myelomonocyte **interferon**-gamma as an effective ingredient.

SUMM As described in Shigeyasu Kobayashi, "**Interferon**", published by Kodansha Co., Ltd., Tokyo, Japan (1975), D. A. J. Tyrrell, "**Interferon** and its Clinical Potential", published by William Heinemann Medical Books Ltd., London (1976), and Protein, Nucleic Acid and Enzyme, Vol.21, No.4, pp.245-333 (1976), **interferon** is a name to designate glycoproteins that are extracellularly inducible in viable cell by subjecting it to the action of an **interferon inducer**, for example, virus, bacterium, protozoon, **rickettsia**, nucleic acid, endotoxin and polysaccharide, as well as having an activity of nonspecifically inhibiting viral growth.

SUMM This activity has rendered **interferons** since the discovery a potential prophylactic and therapeutic agent for viral diseases. Recent studies revealed that **interferons** exert an antioncotic activity on viral tumors, as well as on nonviral tumors. Because of the activity, the development of pharmaceuticals using **interferons** is in great expectation.

SUMM **Interferons** include **interferon**-alpha (or leukocyte **interferon**), **interferon-beta** (or fibroblast **interferon**), and **interferon**-gamma (or immune **interferon**). Preparation of **interferon**-alpha and **interferon-beta** has been established by using leukocyte and fibroblast cell. Recently, pharmaceuticals incorporated with these **interferons** have been commercialized.

SUMM Respective **interferon** will hereinafter be abbreviated as "IFN-alpha", "IFN-beta" and "IFN-gamma" occasionally with the prefix "Hu" representing human origin.

DETD . . . as epidemic conjunctivitis, herpetic keratitis, influenza, rubella, serum hepatitis, and acquired immune deficiency syndrome (AIDS); and nonviral diseases including malignant **tumors** such as **colon** carcinoma, lung carcinoma, liver carcinoma and **osteosarcoma**, and immunopathies including atopic allergy, myoasthenia, collagenosis, pernicious anemia, articular rheumatism, and systemic lupus erythematosus.

DETD . . . and therapeutic agent for viral disease such as those in small and large intestines, as well as that for malignant **tumors** such as **colon** carcinoma and liver carcinoma, and immunopathies such as atopic allergy, pernicious anemia, articular rheumatism, and systemic lupus erythematosus.

CLM What is claimed is:

1. A process for preparing a human myelomonocyte **interferon**-gamma, comprising: propagating an established human myelomonocyte which produces myelomonocyte **interferon**-gamma; and recovering and purifying the **interferon**-gamma produced by said myelomonocyte.

. . . claim 1, wherein said established human myelomonocyte is obtained by: implanting an established human myelomonocyte capable of producing human myelomonocyte **interferon**-gamma in a non-human warm-blooded animal, or inoculating the established human myelomonocyte in a diffusion chamber placed inside or outside the. . .

L14 ANSWER 14 OF 19 USPATFULL

AN 96:31583 USPATFULL
TI Method for treating biological damage using a free-radial scavenger and interleukin-2
IN Zimmerman, Robert, Lafayette, CA, United States
Marafino, Jr., Benedict J., San Francisco, CA, United States
PA Cetus Oncology Corporation, Emeryville, CA, United States (U.S. corporation)
PI US 5508031 960416
AI US 94-289844 940812 (8)
RLI Continuation of Ser. No. US 93-49070, filed on 16 Apr 1993, now abandoned which is a continuation of Ser. No. US 90-626975, filed on 12 Dec 1990, now abandoned which is a division of Ser. No. US 89-399386, filed on 25 Aug 1989, now patented, Pat. No. US 4985241 which is a continuation of Ser. No. US 87-113643, filed on 26 Oct 1987, now abandoned which is a continuation-in-part of Ser. No. US 86-933475, filed on 21 Nov 1986, now abandoned
DT Utility
EXNAM Primary Examiner: Walsh, Stephen G.
LREP Gass, David A.; Savereide, Paul B.; Blackburn, Robert P.
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1581
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Damage to cells, tissue and other body parts in a mammalian host may be treated by using a lymphokine or cytotoxin in conjunction with at least one biological modifier, which may be a free radical scavenger or a metabolic inhibitor. The biological modifier is preferably uric acid, buthionine sulphoximine, vitamin C, aspirin, or nordihydroguaiaretic acid. Such a combination may be used to treat, for example, cancer, infectious diseases, and damage caused by radiation therapy, high oxygen tension, and chemotherapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM Lymphokines and cytotoxins, such as interleukin-2, **interferon**-alpha, **interferon**-gamma, colony stimulating factor, and tumor necrosis factor, are proteins secreted by T cells and/or macrophages upon activation by antigens or. . .
SUMM **Interferons** (IFN) constitute a group of naturally occurring proteins which are known to exhibit anti-viral, anti-tumor and immunoregulatory behavior. Two types. . . IFN have been identified based on differences in their observed biological properties and molecular structures: Type I and Type II. Beta-**interferon** (IFN-.beta.) is a Type I IFN which can be induced in fibroblasts by viral challenge and contains about 165 amino. . .
SUMM . . . Kreuzes)) or with augmentation of natural killer activity (Svedersky et al., J. Immunol. (1984), 133:714-718 and Shalaby et al., J. **Interferon** Res. (1985), 5:571-581). In addition, U.S. Statutory Invention Reg. No. H22, published Feb. 4, 1986 to Creasey et al., discloses. . . in combination therapy of certain breast cancer and myeloma cell lines using synergistically effective amounts of 5-fluorouracil and human recombinant beta-**interferon**. Furthermore, enhanced anti-tumor activity has been observed using IFN-.gamma. in combination with TNF and chemotherapeutic agents. Svedersky et al., Internl.. . .
DETD . . . foreign agents such as pathogens in the cell. Examples of such lymphokines and cytotoxins include, but are not limited to, **interferons** (e.g., **interferon**-alpha, (IFN-.alpha.), **interferon-beta**, (IFN-.beta.), and **interferon**-gamma, (IFN-.alpha.)), interleukins (e.g., interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-3 (IL-3), and interleukin-4 (IL-4)), tumor necrosis factor-alpha (TNF-.alpha.), tumor necrosis factor-beta (TNF-.beta.). . .

. . . . inhibitory activity factor (MIF), macrophage-activating factor (MAF), NK cell activating factor, T cell replacing factor, leukocyte-inhibitory factor (LIF), other lymphotoxins, **osteoclast**-activating factor (OAF), soluble immune response suppressor (SIRS), growth-stimulating factor, a monocyte growth factor, etc. Preferably, the lymphokine or cytotoxin is an interleukin (more preferably IL-2), an **interferon** (more preferably IFN-.beta.), TNF-.alpha. or -.beta., or a colony stimulating factor (more preferably CSF-1). The most preferred herein is TNF-.alpha..

DETD . . . term "cancer" as used in the above definition refers to any neoplastic disorder, including such cellular disorders as, for example, **renal** cell **cancer**, Kaposi's sarcoma, chronic leukemia, breast cancer, sarcoma, ovarian carcinoma, rectal cancer, throat **cancer**, melanoma, **colon cancer**, bladder **cancer**, mastocytoma, lung cancer and gastrointestinal or stomach cancer. Preferably, the **cancer** is **colon cancer**, melanoma, **renal** cell **cancer**, sarcoma, lung cancer, adenocarcinoma, or breast cancer.

DETD The typical dosage level of **interferon** (especially INF-.beta.) in humans ranges from about 100 units to one billion units/m.sup.2. Preferably, IFN-.beta. is administered to humans in. . .

DETD . . . anti-tumor effect in animals and humans. The preclinical response of TNF alone correlated with a clinical response of TNF to **colon cancer**.

DETD . . . Levels Correlate With TNF Resistance In Vivo

Tumor Line	.mu.M Total Glutathione Equivalents/10.sup.6 cells	% Tumor Growth Inhibition.sup.a
PAN-02 (mouse **tumor**)	484 .+-. 90	0
HT29 (human **colon** tumor)	308 .+-. 131	9
P815 (mouse tumor)	305 .+-. 197	20
P388 (mouse tumor)	280 .+-. 150	15
B-16 (mouse tumor)	180 .+-.. . .	

L14 ANSWER 15 OF 19 USPATFULL

AN 94:97330 USPATFULL

TI Human myelomonocyte **interferon**-gamma, and process for preparation and use thereof

IN Kurimoto, Masashi, Okayama, Japan
Mitsuhashi, Masakazu, Okayama, Japan

PA Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Okayama, Japan (non-U.S. corporation)

PI US 5362490 941108

AI US 93-62323 930517 (8)

RLI Continuation of Ser. No. US 91-658740, filed on 22 Feb 1991, now abandoned which is a continuation-in-part of Ser. No. US 87-78005, filed on 21 Jul 1987, now abandoned And a continuation-in-part of Ser. No. US 89-379318, filed on 13 Jul 1989, now abandoned

PRAI JP 86-176266 860725
JP 87-125777 870525
JP 88-184069 880725

DT Utility

EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Bugaisky, Gabriele E.
LREP Browdy and Neimark
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1185
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a novel human **interferon**-gamma derived from an established human myelomonocyte, a process to prepare said **interferon**-gamma, and its use. The human myelomonocyte **interferon**-gamma has a novel polypeptide and carbohydrate chain structure, and it is effective in preventing and treating viral diseases, malignant tumors and immunopathies alone or in combination with other lymphokine and/or chemotherapeutic.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Human myelomonocyte **interferon**-gamma, and process for preparation and use thereof
AB The present invention relates to a novel human **interferon**-gamma derived from an established human myelomonocyte, a process to prepare said **interferon**-gamma, and its use. The human myelomonocyte **interferon**-gamma has a novel polypeptide and carbohydrate chain structure, and it is effective in preventing and treating viral diseases, malignant tumors. . .
SUMM The present invention relates to a novel human myelomonocyte **interferon**-gamma, a process for preparing this **interferon**-gamma, and its use.
SUMM More particularly, the present invention relates to a novel human myelomonocyte **interferon**-gamma, and a process for preparing this **interferon**-gamma, characterized by allowing an established human myelomonocyte capable of producing myelomonocyte **interferon**-gamma to produce the **interferon**-gamma, and recovering the accumulation; a process for preparing a monoclonal anti-**interferon**-gamma antibody using the myelomonocyte; and a method for purifying the **interferon**-gamma using the monoclonal antibody, as well as to a prophylactic and therapeutic agent for **interferon**-gamma susceptible disease, these agents containing the human myelomonocyte **interferon**-gamma as an effective ingredient thereof.
SUMM As described in Sigeyasy Kobayashi, "**Interferon**", published by Kodansha Co., Ltd. Tokyo, Japan (1975), D. A. J. Tyrrell, "**Interferon** and its Clinical Potential", published by William Heinemann Medical Books Ltd., London (1976), and Protein, Nucleic Acid and Enzyme, Vol. 21, No. 4, pp. 245-333 (1976), **interferon** is a name used to designate glycoproteins that can be extracellularly induced in a viable cell by subjecting the cell to the action of an **interferon inducer**, such as a virus, a bacterium, a protozoon, **rickettsia**, nucleic acid endotoxin, or polysaccharide. These glycoproteins also are capable of nonspecifically inhibiting viral growth.
SUMM This activity has made **interferons** potential prophylactic and therapeutic agents for viral diseases. Recent studies revealed that **interferons** exert an antioncotic activity on viral tumors, as well as on nonviral tumors. Because of the activity of **interferons**, there is much interest in developing pharmaceuticals using **interferons**.
SUMM **Interferons** include **interferon**-alpha (or leukocyte **interferon**), **interferon-beta** (or fibroblast **interferon**), and **interferon**-gamma (or immune **interferon**). Preparation of **interferon**-alpha and **interferon-beta**

has been effected by using leukocytes and fibroblast cells. Recently, pharmaceuticals containing these **interferons** have been commercialized.

SUMM The **interferons** hereinafter will be abbreviated as "IFN-alpha", IFN-beta", and "IFN-gamma", occasionally with the prefix "Hu" indicating human origin.

DETD . . . conjunctivitis, herpetic keratitis, influenza, rubella, serum hepatitis, and acquired immune deficiency syndrome (AIDS); as well as nonviral diseases including malignant **tumors** such as **colon** carcinoma, lung carcinoma, liver carcinoma and **osteosarcoma**; immunopathies including atopic allergy, myasthenia, collagenosis, pernicious anemia, articular rheumatism, and systemic lupus erythematosus.

DETD . . . and therapeutic treatment of viral diseases such as those in the small and large intestines, as well as for malignant **tumors** such as **colon** carcinoma and liver carcinoma, and immunopathies such as atopic allergy, pernicious anemia, articular rheumatism, and systemic lupus erythematosus.

CLM What is claimed is:

1. A prophylactic and therapeutic composition for human **interferon**-gamma-susceptible diseases comprising an effective amount of human myelomonocyte **interferon**-gamma for preventing or treating said human **interferon** -gamma-susceptible diseases and a pharmaceutically acceptable carrier.

2. The composition of claim 1 wherein said human myelomonocyte **interferon**-gamma is produced by: propagating an established human myelomonocyte which produces myelomonocyte **interferon**-gamma and recovering and purifying the **interferon**-gamma produced by said myelomonocyte.

. . . claim 2 wherein said established human myelomonocyte is produced by: implanting an established human myelomonocyte capable of producing human myelomonocyte **interferon**-gamma in a non-human warm-blooded animal; and allowing said established human myelomonocyte to proliferate while allowing said established human myelomonocyte to. . .

5. The composition of claim 2 wherein said human myelomonocyte **interferon**-gamma is purified by column chromatography using an anti-**interferon**-gamma antibody.

9. The composition of claim 1 in which said human myelomonocyte **interferon**-gamma is present in the range of 1-10,000 units/g.

11. The composition of claim 1 wherein said lymphokine is selected from the group consisting of **interferon**-alpha, **interferon-beta**, tumor necrosis factor, lymphotoxin, interleukin 2, B-cell differentiating factor, and mixtures thereof.

12. A human myelomonocyte **interferon**-gamma.

13. The human myelomonocyte **interferon**-gamma of claim 12 which is obtained by: propagating an established human myelomonocyte which produces myelomonocyte **interferon** -gamma; and recovering and purifying the **interferon** -gamma produced by said myelomonocyte.

14. The human myelomonocyte **interferon**-gamma of claim 13, wherein said established human myelomonocyte is obtained by: implanting an established human myelomonocyte capable of producing human myelomonocyte **interferon**-gamma in a non-human warm-blooded animal or inoculating the established human

myelomonocyte capable of producing human myelomonocyte **interferon**-gamma into a diffusion chamber placed inside or outside the body of a non-human warm-blooded animal; and allowing the established human. . .

15. The human myelomonocyte **interferon**-gamma of claim 13 wherein said established human myelomonocyte is selected from the group consisting of HBL-38 cells, HL-60 cells (ATCC. . .

16. The human myelomonocyte **interferon**-gamma of claim 13 wherein said **interferon**-gamma is purified by column chromatography using an anti-**interferon**-gamma antibody.

17. The human myelomonocyte **interferon**-gamma of claim 13, wherein said established human myelomonocyte is contacted with an inducer.

18. The human myelomonocyte **interferon**-gamma of claim 17 wherein said inducer is selected from the group consisting of phytohemagglutinin, concanavalin A, pokeweed mitogen, lipopolysaccharide, lipid. . .

19. A method for treating diseases which are susceptible to treatment by human myelomonocyte **interferon**-gamma comprising administering to a patient suffering from a disease which is susceptible to treatment by human myelomonocyte **interferon**-gamma an effective amount to treat said disease which is susceptible to such treatment of a composition according to claim 1.

. . .

22. The method according to claim 21 wherein said lymphokine is selected from the group consisting of **interferon**-alpha, **interferon-beta**, tumor necrosis factor, lymphotoxin, interleukin 2, B cell differentiating factor, and mixtures thereof.

L14 ANSWER 16 OF 19 USPATFULL
AN 92:53099 USPATFULL
TI Process to prepare metastasis-inhibitory factor
IN Kurimoto, Masashi, Okayama, Japan
Motoda, Ryuichi, Okayama, Japan
Iwaki, Kanso, Okayama, Japan
PA Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Okayama, Japan (non-U.S. corporation)
PI US 5126148 920630
AI US 90-526143 900522 (7)
PRAI JP 89-128362 890522
DT Utility
EXNAM Primary Examiner: Robinson, Douglas W.; Assistant Examiner: Witz, Jean C.
LREP Browdy and Neimark
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 461
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Human hematopoietic cells produce metastasis-inhibitory factor (MIF). MIF exhibits a remarkable metastasis-inhibitory activity on viral diseases and immunopathies, as well as on malignant tumors. The MIF-producing human hematopoietic cells are easily proliferative by in vitro tissue culture and in vivo proliferation using a non-human warm-blooded animal. T cells exhibit a high MIF producibility. Mitogens augment the production of MIF when used as an MIF inducer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . we found that metastasis-inhibitory substances can be

screened by checking them with RPMI 4788 cell (FERM BP-2429), an established human **colon cancer** cell, for their metastasis-inhibitory activity. Furthermore, we established a process to prepare MIF which comprises allowing an established human hematopoietic. . .

SUMM . . . epidemic conjunctivitis, herpetic keratitis, influenza, rubella, serum hepatitis and acquired immune deficiency syndrome (AIDS); and non-viral diseases, for example, malignant **tumors** including **colon cancer**, lung **cancer**, liver cancer and **osteosarcoma**, and immunopathies such as atopic allergy, myastheniagravis, collagen disease, malignant anemia, articular rheumatism and systemic lupus erythematodus.

SUMM . . . of MIF. If necessary, they can be incorporated with one or more lymphokines, and/or natural or synthetic chemotherapeutics, for example, **interferon**-.alpha., **interferon**-.**beta**., **interferon**-.gamma., tumor necrosis factor, lymphotoxin, interleukin 1, interleukin 2 and B-cell differentiating factor, in order to augment their prophylactic and therapeutic. . .

SUMM . . . (1987) with a slight modification, wherein a lung metastasis is induced with RPMI 4788 cell (FERM BP-2429), an established human **colon cancer** cell, in nude mice which are then administered with a liquid sample containing MIF to determine its metastasis-inhibitory activity.

SUMM . . . of MIF that halves the number of nodules, provided that the control forms 100 or more nodules under these conditions. **Interferon**-.alpha., **interferon**-.**beta**., **interferon**-.gamma., tumor necrosis factor-.alpha., tumor necrosis factor-.beta., interleukin 1 and interleukin 2 are removed from the liquid sample prior to its. . .

SUMM The product suppresses, in addition to the lung metastasis of RPMI 4788 cell, a human **colon cancer** cell, the liver metastasis of Lovo cell (ATCC CCL 229), a human **colon cancer** cell.

CLM What is claimed is:

. . . the obtained fraction to gel filtration chromatography and recovering the fraction with a molecular weight of 10,000-450,000; and removing any **interferon**-.alpha., **interferon** -.**beta**., **interferon**-.gamma., tumor necrosis factor-.alpha., tumor necrosis factor-.beta., interleukin 1 and interluekin 2, whereby a fraction is obtained which is rich in MIF which exhibits metastasis-inhibitory activity when assayed with an established human **colon cancer** cell, RPMI 4789 (FERM BP-2429).

L14 ANSWER 17 OF 19 USPATFULL

AN 91:4937 USPATFULL

TI Therapeutic combination of free-radical scavenger and tumor necrosis factor

IN Zimmerman, Robert, Lafayette, CA, United States
Marafino, Jr., Benedict J., San Francisco, CA, United States

PA Cetus Corporation, Emeryville, CA, United States (U.S. corporation)

PI US 4985241 910115

AI US 89-399386 890825 (7)

RLI Continuation of Ser. No. US 87-113643, filed on 26 Oct 1987, now abandoned which is a continuation-in-part of Ser. No. US 86-933475, filed on 21 Nov 1986, now abandoned

DT Utility

EXNAM Primary Examiner: Draper, Garnette D.

LREP Giotta, Gregory J.; Hasak, Janet E.; Halluin, Albert P.

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 1333
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Damage to cells, tissue and other body parts in a mammalian host may be treated by using a lymphokine or cytotoxin in conjunction with at least one biological modifier, which may be a free radical scavenger or a metabolic inhibitor. The lymphokine or cytotoxin is preferably tumor necrosis factor and the biological modifier is preferably uric acid, buthionine sulphoximine, vitamin C, aspirin, or nordihydroguaiaretic acid. Such a combination may be used to treat, for example, cancer, infectious diseases, and damage caused by radiation therapy, high oxygen tension, and chemotherapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM Lymphokines and cytotoxins, such as interleukin-2, **interferon**-alpha, **interferon**-gamma, colony stimulating factor, and tumor necrosis factor, are proteins secreted by T cells and/or macrophages upon activation by antigens or. . .

SUMM **Interferons** (IFN) constitute a group of naturally occurring proteins which are known to exhibit anti-viral, anti-tumor and immunoregulatory behavior. Two types. . . IFN have been identified based on differences in their observed biological properties and molecular structures: Type I and Type II. Beta-**interferon** (IFN-.beta.) is a Type I IFN which can be induced in fibroblasts by viral challenge and contains about 165 amino. . .

SUMM . . . Kreuzes)) or with augmentation of natural killer activity (Svedersky et al., J. Immunol. (1984), 133:714-718 and Shalaby et al., J. **Interferon** Res. (1985), 5:571-581). In addition, U.S. Statutory Invention Reg. No. H22, published Feb. 4, 1986 to Creasey et al., discloses. . . in combination therapy of certain breast cancer and myeloma cell lines using synergistically effective amounts of 5-fluorouracil and human recombinant beta-**interferon**. Furthermore, enhanced anti-tumor activity has been observed using IFN-.gamma. in combination with TNF and chemotherapeutic agents. Svedersky et al., Internl.. . .

DETD . . . foreign agents such as pathogens in the cell. Examples of such lymphokines and cytotoxins include, but are not limited to, **interferons** (e.g., **interferon**-alpha, (IFN-.alpha.), **interferon-beta**, (IFN-.beta.), and **interferon**-gamma, (IFN-.alpha.)), interleukins (e.g., interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-3 (IL-3), and interleukin-4 (IL-4)), tumor necrosis factor-alpha (TNF-.alpha.), tumor necrosis factor-beta (TNF-.beta.). . . inhibitory activity factor (MIF), macrophage-activating factor (MAF), NK cell activating factor, T cell replacing factor, leukocyte-inhibitory factor (LIF), other lymphotoxins, **osteoclastactivating** factor (OAF), soluble immune response suppressor (SIRS), growth-stimulating factor, a monocyte growth factor, etc. Preferably, the lymphokine or cytotoxin is an interleukin (more preferably IL-2), an **interferon** (more preferably IFN-.beta.), TNF-.alpha. or -.beta., or a colony stimulating factor (more preferably CSF-1). The most preferred herein is TNF-.alpha..

DETD . . . term "cancer" as used in the above definition refers to any neoplastic disorder, including such cellular disorders as, for example, **renal** cell **cancer**, Kaposi's sarcoma, chronic leukemia, breast cancer, sarcoma, ovarian carcinoma, rectal cancer, throat **cancer**, melanoma, **colon cancer**, bladder **cancer**, mastocytoma, lung cancer and gastrointestinal or stomach cancer. Preferably, the **cancer** is **colon cancer**, melanoma, **renal** cell **cancer**, sarcoma, lung cancer, adenocarcinoma, or breast cancer.

DETD The typical dosage level of **interferon** (especially INF-.beta.) in humans ranges from about 100 units to one billion units/m.sup.2 Preferably, IFN-.beta. is administered to humans in. . .

DETD . . . anti-tumor effect in animals and humans. The preclinical response of TNF alone correlated with a clinical response of TNF to **colon cancer**.

DETD . . . Correlate With TNF Resistance In Vivo

Tumor Line	.mu.M total Glutathione Equivalents/ 10.sup.6 cells	% Tumor Growth Inhibition.sup.a
PAN-02 (mouse **tumor**)	484 .+-. 90	0
HT29 (human **colon** tumor)	308 .+-. 131	9
P815 (mouse tumor)	305 .+-. 197	20
P388 (mouse tumor)	280 .+-. 150	15
B-16 (mouse tumor)	180 .+-.. . .	

L14 ANSWER 18 OF 19 USPATFULL
AN 90:42339 USPATFULL
TI Method of treating **interferon** sensitive diseases, and a method and device for preparing .gamma.-**interferon** containing preparation
IN Lindblom, Ragnvald E., Alsater, S-740 10 Almunge, Sweden
Rothman, Ulf S., Box 120, S-230 10 Skanor, Sweden
PI US 4929443 900529
AI US 87-50470 870518 (7)
RLI Continuation of Ser. No. US 85-711567, filed on 13 Feb 1985, now abandoned which is a continuation of Ser. No. US 83-503575, filed on 13 Jun 1983, now abandoned
DT Utility
EXNAM Primary Examiner: Hazel, Blondel
LREP Bacon & Thomas
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 302
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods and means for treating **interferon**-sensitive diseases are disclosed, wherein a whole blood sample is taken from a patient suffering from such disease and is incubated in vitro together with a mitogen to produce .gamma.-**interferon**. After incubation the whole blood sample is subjected to a separation step for producing a blood plasma product, which is free from the mitogen but contains .gamma.-**interferon**. This blood plasma product is used for re-administration to the patient from which the whole blood sample was taken.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Method of treating **interferon** sensitive diseases, and a method and device for preparing .gamma.-**interferon**

containing preparation

AB Methods and means for treating **interferon**-sensitive diseases are disclosed, wherein a whole blood sample is taken from a patient suffering from such disease and is incubated in vitro together with a mitogen to produce .gamma.-**interferon**. After incubation the whole blood sample is subjected to a separation step for producing a blood plasma product, which is free from the mitogen but contains .gamma.-**interferon**. This blood plasma product is used for re-administration to the patient from which the whole blood sample was taken.

SUMM The present invention relates to a novel method of producing **interferon**, a novel method of treatment for preventing and treating **interferon** sensitive diseases and novel means for carrying out these methods.

SUMM **Interferons** are proteinaceous substances which are induced intra cellularly or extra cellularly upon exposure of the cells to **interferon** inducing agents such as viruses, bacteria, protozoes, **rickettsia**, nucleic acids, endotoxines, polysaccharides, etc.

SUMM **Interferons** have a great potential interest as drugs since they unspecifically inhibit the growth of various viruses in the cells, have. . .

SUMM However, the development of **interferon** as a drug is severely inhibited by the great difficulties in preparing the necessary amounts, i.a. depending on the fact that **interferon** is species specific. Thus, only **interferon** originating from live human cells is useful for human therapy. For the preparation of **interferon** human leukocytes and the like are conventionally used, and the very limited supply of such starting material is a great. . .

SUMM Attempts have also been made to prepare **interferon** in vitro by culturing established human cells on a nutrient medium in the presence of various **interferon** inducers. However, not either this method has given the desired results.

SUMM In recent years it has been established that human **interferon** exists in at least three different molecular variants, viz. .alpha.-**interferon** (previously called leukocyte **interferon**), .**beta**.-**interferon** (previously fibroblast **interferon**), and .gamma.-**interferon** (previously immune **interferon**).

SUMM It is further known from numerous publications that many substances induce the formation of **interferons**. Thus, .alpha.- and .beta.-**interferon** are induced by viruses, and .gamma.-**interferon** by so called mitogens and antigens.

SUMM .gamma.-**interferon** is believed to have a tremendeous potential as an agent for treating **interferon**-sensitive diseases, such as tumours. However, .gamma.-**interferon** is difficult to produce and is unstable, and attempts to stabilize it have so far been unsuccessful.

SUMM The present invention suggests a new approach to the problem of preparing and using .gamma.-**interferon** for treating **interferon**-sensitive diseases. A first aspect of the invention is based on the per se well known fact that mitogens induce the production of .gamma.-**interferon**, and in accordance with this aspect of the invention .gamma.-**interferon** production is induced by incubating whole blood samples from a patient to be treated with one or more mitogens in. . . incubation has been terminated the incubated blood sample is subjected to a separation step to produce a plasma containing the **interferon** produced but not the mitogen. The incubation and separation steps are performed in vitro.

SUMM In a second aspect of the invention the (.gamma.) **interferon**-containing plasma is then re-administered to

the same patient, who will thus receive an **interferon** preparation which does not only originate from the same species (a human) but from the same individual (himself/herself): the preparation. . . following: a very simple, rapid and inexpensive production of the preparation, elimination or considerable reduction of the instability problems with .gamma.-**interferon**, reduced side effects because of the individual specificity, etc.

SUMM It is essential to separate the mitogen before re-administering the **interferon** containing plasma to the patient. For this separation any suitable conventional separation technique can be used, provided that the same. . . capable of separating all of the mitogen from the plasma product while leaving a therapeutically effective amount of the produced **interferon** therein. The separation technique can be based on the physical and/or biological/biochemical properties of the mitogen. Examples of suitable separation. . .

SUMM When using ultrafiltration the cut-off properties of the ultra filter are chosen with regard to the choice of the .gamma.-**interferon** inducing mitogens. Thus, the filter and the mitogens should be chosen such that .gamma.-**interferon** can pass through the filter, whereas the mitogens are excluded, or vice versa. Since the major part of .gamma.-**interferon** has a molecular weight of about 20,000-75,000 (with a minor part having a molecular weight of about 65,000-70,000) the filter. . . at least 50,000 to pass through, when the mitogen has a molecular weight which is higher than that of the **interferon**. The upper cut-off limit is chosen with regard to the molecular weight of the mitogen used. Obviously the mitogen must. . . permitting a cut-off value of the filter of e.g. about 100,000, which also permits the minor part (see above) of .gamma.-**interferon** to pass through the filter. Mitogens having comparatively low molecular weights, e.g. overlapping the molecular weight range for the **interferon**, can be bound to a suitable matrix to increase the molecular weight and permit separation by ultrafiltration. As mentioned above. . . molecular mitogens can be separated by using a filter having a low cut-off limit permitting the mitogen, but not the **interferon** to pass through.

SUMM The incubation of the whole blood sample with the mitogen (or mitogens) is carried out under conditions promoting .gamma.-**interferon** production, e.g. at a temperature of about 35.degree. to 40.degree. C. and for e.g. at least about 2 or 4. . . to be used depends on the specific mitogen. This amount is chosen so as to produce an optimal amount of .gamma.-**interferon**, and it can easily be established by a person of average skill in the art by simple tests. Excessive amounts of mitogen should be avoided since this may inhibit the **interferon** production. For the preferred mitogen PHA suitable amounts are e.g. from about 1 to about 5 .mu.g PHA per ml. . .

SUMM The preferred mode of administering the **interferon**-containing preparation is by intramuscular injection, but also other routes may be possible, such as intravenous or subcutaneous injection. Where combined treatment with a histamine H2-antagonist is used, the histamine H2-antagonist may be injected together with the .gamma.-**interferon**-containing plasma or it may be administered separately, e.g. by the oral route. The dosage of the histamine H2-antagonist will vary. . .

SUMM It is believed that the effect obtained by means of the **interferon** preparation and treatment in accordance with the invention is a result both of the direct effect of .gamma.-**interferon** as such and on the fact that .gamma.-**interferon** triggers the production of .alpha.- and .beta.-**interferon** in vitro and/or in vivo. It may in this context

be mentioned that .alpha.- and .beta.-**interferon** are capable of passing through the filter together with .gamma.-**interferon** (when using this separation technique). The incubation of the whole blood sample with the mitogen also triggers the production of other lymphokines, which further enhance the effect of the .gamma.-**interferon**-containing blood plasma. In particular the triggered production of interleukins, especially interleukin II (ILII), is believed to give a valuable contribution. . . mentioned diseases. Such lymphokins, especially ILII, can readily be separated from the mitogen in the separation step, together with the **interferons**. For example, ILII has a suitable molecular weight somewhat lower than that of .gamma.-**interferon**.

SUMM In a further aspect of the invention the **interferon**-containing plasma is administered in combination with a histamine H2-antagonist. As is well known, histamine H2-antagonists are compounds which block histamine. . . the invention it has unexpectedly been found that a synergistic effect, in particular a synergistic anti-tumour effect, is achieved when .gamma.-**interferon** is administered together with a histamine H2-antagonist such as cimetidine. The mechanism of this synergistic effect has not been clarified.

DETD The ultrafiltrate obtained was tested as to **interferon** activity in the so-called NK system (as described by Ratliff et al in Cellular Immunology, Vol. 57, Jan. 1, 1981). . .

DETD . . . to stimulate the NK (natural killer) activity of mononuclear blood or spleen cells as an indicator of the presence of gamma-**interferon**. The test was a standard test for NK lymphocyte activity making use of target cells from a very sensitive cell. . . Mononuclear cells of healthy human donor were incubated for 2 hrs at 37.degree. C. with plasma to be tested for **interferon** content, after which the cells were added to K 562 target cells at various ratios and incubated for 4 hrs.. . .

DETD .gamma.-**interferon**-containing rat plasma was prepared as in Example 2, using PHA (available from Pharmacia AB, Uppsala, Sweden) as the mitogen. The .gamma.-**interferon** preparation was injected intramuscularly (21 doses of 0.1-0.4 ml per animal) in combination with a histamine H2-antagonist (cimetidine) to rats which had been challeged subcutaneously with a transplantable DMH-induced colon carcinoma isograft (1.5.times.10.sup.3 viable cells). The rejection of **colon cancer** isograft was evaluated by the number of tumour-free rats after 3, 6 and 13 weeks respectively. The treated rats demonstrated. . .

CLM What is claimed is:

1. A method of treating **interferon** sensitive diseases, comprising the steps of taking a whole blood sample from a human or animal patient suffering from such disease, incubating said whole blood sample in vitro in the presence of a mitogen to produce .gamma.-**interferon**, subjecting said incubated whole blood sample to a separation step so as to produce a blood plasma preparation which is free of said mitogen but contains a therapeutically effective amount of said produced .gamma.-**interferon**, and re-administering said blood plasma preparation to the same patient.

. . . method of claim 1, wherein said incubation of said whole blood sample also produces at least one lymphokin other than **interferon**, and wherein said separation step is carried out so as to retain at least a major part of said at. . .

6. The method of claim 5 wherein the lymphokin other than **interferon** is interleukin II.

L14 ANSWER 19 OF 19 CAPLUS COPYRIGHT 1998 ACS
AN 1997:414214 CAPLUS
DN 127:29081
TI Flow cytometric pharmacosensitivity assay and method of cancer treatment
IN Medenica, Rajko D.; Powell, David K.
PA Medenica, Rajko D., USA
SO PCT Int. Appl., 99 pp.
CODEN: PIXXD2
PI WO 9719189 A1 970529
DS W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 96-US18543 961112
PRAI US 95-559812 951117
DT Patent
LA English
AB A method is disclosed for treating cancer with a multidrug chemotherapeutic regimen detd. by in vitro pharmacosensitivity tests. A cell suspension is prepd. from a tumor specimen obtained from the patent. The viable tumor cell count within the cell suspension is calcd. The vol. of the cell suspension is then adjusted to obtain a base cell concn. by dilg. the cell suspension with patient medium in proportion with the viable tumor cell count. A sample of the cell suspension is retained as a neg. control sample. Drug samples are then prepd., each drug sample contg. a mixt. of cell suspension, patient medium, and a drug selected from several drugs, wherein each drug sample contains a different drug which is added to the drug sample in an aliquot amt. proportional to the base cell concn. The drug samples and neg. control sample are then incubated. After incubation, the drug samples and neg. control sample are stained with a DNA intercalating dye. The cell viability in the drug samples and neg. control sample is detd. by use of a flow cytometer. The cell viability in the drug samples and neg. control sample is compared to det. the pharmacosensitivity of the tumor. A multidrug treatment regimen is then administered to the patient, wherein the regimen includes the drugs shown to be most effective against the tumor in the pharmacosensitivity assay. The treatment has been shown to be esp. useful in the simultaneous treatment of primary tumors and their metastases, esp. when the chemotherapeutic regimen is administered locoregionally by intra-arterial infusion methods.
IT **Interferon** .tau.
Interferon .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(1b; flow cytometric pharmacosensitivity assay and method of cancer treatment)
IT Bladder tumors
Breast tumors
Chronic myelogenous leukemia
Colon tumors
Liver tumors
Lung tumors
Melanoma
Metastasis (tumor)
Metastasis to liver
Myeloid leukemia
Non-Hodgkin's lymphoma
Osteosarcoma
Ovarian carcinoma

Ovarian tumors
Pancreatic tumors
Renal cell carcinoma
Tumors (animal)
(cells; flow cytometric pharmacosensitivity assay and method of cancer treatment)

IT Antitumor agents
Bladder carcinoma inhibitors
Breast tumor inhibitors
Chronic myelogenous leukemia inhibitors
Colon tumor inhibitors
Drug resistance
Flow cytometry
Hepatoma inhibitors
Liver metastasis inhibitors
Lung tumor inhibitors
Melanoma inhibitors
Metastasis inhibitors
Myeloid leukemia inhibitors
Ovarian carcinoma inhibitors
Ovarian tumor inhibitors
(flow cytometric pharmacosensitivity assay and method of cancer treatment)

IT Hormones (animal), biological studies
Interferon .alpha.
Interferon .alpha.2a
Interferon .alpha.2b
Interferon .beta.
Interleukin 2
Tumor necrosis factors
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flow cytometric pharmacosensitivity assay and method of cancer treatment)

IT Non-Hodgkin's lymphoma
Osteosarcoma
Pancreatic tumors
Renal cell carcinoma
(inhibitors; flow cytometric pharmacosensitivity assay and method of cancer treatment)

IT Antitumor agents
(**osteosarcoma**; flow cytometric pharmacosensitivity assay and method of cancer treatment)

IT Metastasis inhibitors
(**renal** cell **cancer**, to liver; flow cytometric pharmacosensitivity assay and method of cancer treatment)

IT **Interferons**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.pi.; flow cytometric pharmacosensitivity assay and method of cancer treatment)